The Journal of Pediatrics

VOL. 26 JUNE, 1945 NO. 6

Original Communications

CONGENITAL ALKALOSIS WITH DIARRHEA

JAMES L. GAMBLE, M.D., KATHLEEN R. FAHEY, A.B., JANET APPLETON, A.B., AND ELSIE MACLACHLAN, B.S.

BOSTON, MASS.

CONTINUED loss of gastric secretions by vomiting is a well-known cause of alkalosis. The much larger removal of chloride than of sodium produces reduction of chloride concentration in extracellular fluid with corresponding extension of bicarbonate. The alkalosis of vomiting is thus easily understandable. Severe diarrhea causes wastage of all of the gastrointestinal secretions. The secretions which enter the intestine contain more of sodium than of chloride and their total volume is several times larger than the volume of gastric juice. It is, therefore, to be expected that diarrheal stools will contain a larger quantity of sodium than of chloride. The concentrations of these two ions in the gastrointestinal secretions are shown by the diagrams in Fig. 1, and also values which have been found in diarrheal stools. It is evident from these data that diarrhea would not be expected to cause recession of chloride in the plasma with resulting alkalosis. Actually, in severe diarrheal disease, unless vomiting is a prominent feature, reaction change in extracellular fluid has been found to be in the direction of acidosis which is often of severe degree.

This paper presents data obtained from an infant who directly disobeyed these simple and apparently axiomatic rules for diarrheal disease. This patient, O. C., was 14 months of age when he entered the hospital. His affliction was a voluminous watery diarrhea which began directly after birth and had steadily continued. There was no evidence of impairment of gastric function. A large intake of milk supplemented by various other suitable articles of food was accepted without vomiting. Measurements of plasma chloride unexpectedly revealed persistently low values. The bicarbonate concentration was greatly extended beyond its normal value and plasma pH was increased. The lowest value found for chloride was 44 meq./L. which is less than one-half of the usual value (100 meq./L.). The accompanying bicarbonate measurement was 61 meq./L. which is more than double the normal value, which for an infant may be taken as 25 meq./L. In the more usual form of statement, the plasma bicarbonate was on this occasion 134 volumes per cent. Plasma pH was 7.64. These measurements describe an alkalosis of exceptionally severe degree. This unorthodox combination of alkalosis and diarrhea in the absence of vomiting suggested analysis of the stools for chloride and sodium. A large excess of chloride over sodium was found. Measurements of the outgo of

From the Department of Pediatrics, Harvard Medical School and the Infants' and Children's Hospitals.

chloride and sodium in the urine and stools of this patient over a twenty-four-hour period are recorded in the second section of Fig. 2. To permit comparison with the usual findings, measurements from another infant (R. W.) suffering from diarrhea of about the same degree as measured by stool volume are presented in the first section of the chart. They show the expected much larger loss of Na than of Cl in the stools and in consequence limitation of Na outgo in the urine in defense of the sodium balance of the body. These findings are reversed for the nonconformist patient, O. C.; practically all of the Cl outgo is in the stools and is enormously in excess of Na.

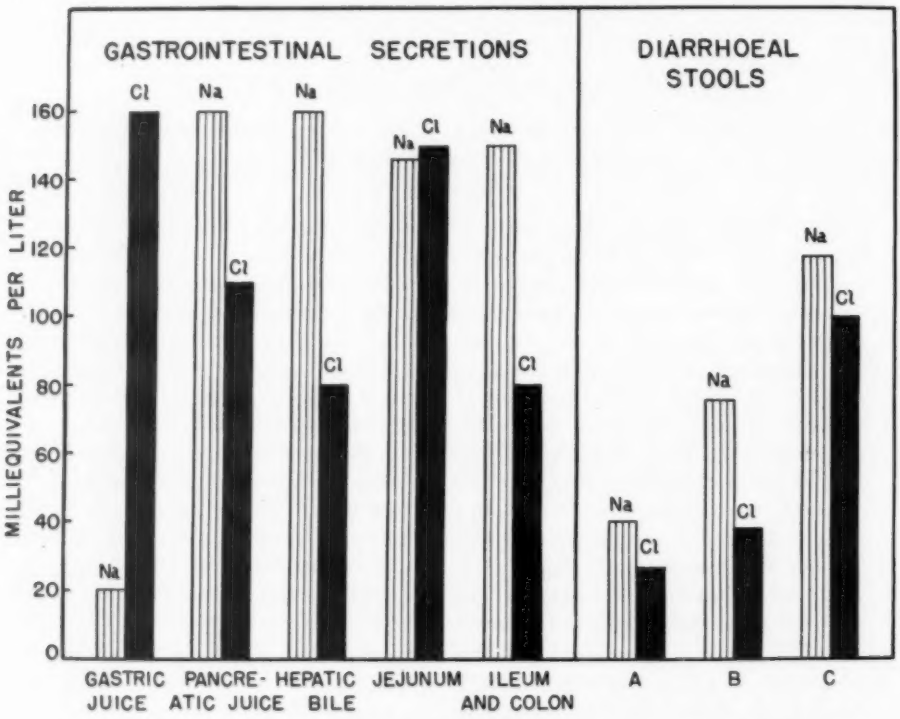

Fig. 1.—Sodium and chloride in gastrointestinal secretions and in diarrheal stools. *A*, average values found in severe diarrhea, stool volume 300 c.c., by Holt, Courtney and Fales.[1] *B*, values at a stool volume of 500 c.c. *C*, values found in absence of food intake, stool volume 250 c.c. *B* and *C*, single observations by authors.

According to the diagrams in Fig. 1, secretion of an abnormally large volume of gastric juice might explain the Cl excess in the stools. Owing to the relatively very small quantity of Na in the juice, an increased secretion might conceivably be of an extent which would produce a larger content of Cl than of Na in the mixture of gastric and intestinal secretions lost in the stools. No evidence of hypersecretion was found. At least in the fasting state, secretion was more scanty than usual and was not greatly increased by histamine. Duodenal secretions were found to have a usual composition as regards Na and Cl. Measurements from three separate collections were as follows: Na, meq./L., 155, 152, 154 and Cl, meq./L., 94, 74, 107. The possibility of abnormal secretions in the lower reaches of the intestinal tract was not explored. No evidence of an anatomic defect connecting the stomach with the large bowel was found. Carmine placed in the food did not appear in the stools until after

an interval of from four to eight hours. Aberrant gastric mucosa somewhere in the intestinal tract would provide a direct explanation of chloride excess in the stools. This possibility was under consideration from the outset of study of this patient and was supported by slight x-ray evidence of malformation of the tract. After a year of unsuccessful inquiry during which there was no abatement of the diarrhea and no gain in nutritional status, it was decided that surgical exploration was justifiable. No reduplication or diverticulum of the intestinal tract was found. Following exploration a fatal obstruction developed. Careful search post mortem failed to reveal aberrant gastric mucosa.*

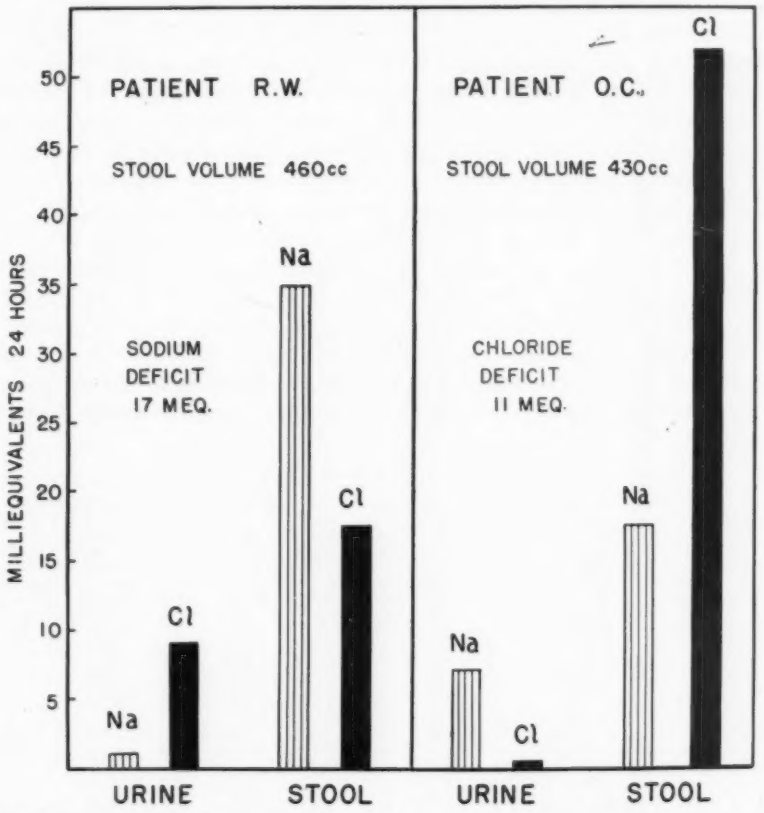

Fig. 2.—Sodium and chloride outgo in urine and stools. Measurements from patient R. W. illustrate usual findings, which are reversed for the atypical patient O. C.

MEASUREMENTS

Diarrhea is clearly not the primary cause of the chloride excess in the stools and the accompanying reduction of chloride and extension of bicarbonate in the blood plasma found for this infant. In the absence of a simple anatomic explanation it would seem to be evident that the underlying cause must be an intrinsic defect in the government of electrolyte distribution in the body fluids. Obviously this defect is not easily accessible to study. As a first step it was undertaken to describe its visible effects by repeated measurements in the

*We are indebted to Dr. Sidney Farber for establishing the absence of aberrant gastric mucosa by an extremely careful search throughout the intestinal tract.

blood plasma and in the urine and stools of the electrolytes which are prominent in the ionic structure of the body fluids and in allocation of water to the extra- and intracellular compartments. From these measurements data for gain or loss of these body fluid components were obtained at various levels of supply over periods of from three to four days. This first step was accomplished in considerable detail. Quantitative description of the effects of the hidden disturbance of body fluid physiology in this infant is the substance of this report.

Selected examples of plasma data are recorded in Table I. After food intake was established at an ample level, plasma chloride rose to a position which oscillated between 70 and 80 meq./L., and there was roughly corresponding reduction of total CO_2. Partition of total CO_2 into its components, carbonic acid and bicarbonate, reveals approximately normal values for (H_2CO_3). Taking 25 meq./L. as the usual total CO_2 value for an infant, (H_2CO_3) at pH 7.4 is 1.2 meq./L. With increase of $(BHCO_3)$ there is usually increase of (H_2CO_3) by respiratory adjustment, which greatly limits change in pH. By way of instance, complete compensation for the $(BHCO_3)$ value 46.1 meq./L., found for plasma No. 5, would require an increase of (H_2CO_3) to 2.2 meq./L.; change to this extent would preserve the physiologically correct pH, 7.4. Instead, (H_2CO_3) remains at the normal value and the change in bicarbonate is permitted to raise pH to 7.65. It is evident from these measurements of (H_2CO_3) that this infant presented an uncompensated alkalosis. As a curious companion feature it may be mentioned that there was no clinical evidence of physiologic disadvantage from the alkalosis which according to plasma pH was of very severe degree. Discernible signs of tetany were at no time present.*

TABLE I. DATA FROM PLASMA

PLASMA NO.	REGIME	Na meq./L.	Cl meq./L.	CO_2 meq./L.	pH	H_2CO_3* meq./L.	$BHCO_3$* meq./L.	BALANCE PERIOD†
1	Similac	134	56					I (i)
2	Similac	137	44	61.0	7.60	1.9	59.1	I (f)
3	Milk	138	74	42.1	7.62	1.2	40.9	
4	Milk	143	78	43.7	7.62	1.2	42.5	
5	Milk	136	72	47.3	7.65	1.2	46.1	
6	Milk NaCl, 3 Gm.	139	86	31.6	7.52	1.2	30.4	
7	Milk NaCl, 3 Gm.	138	88	36.5	7.48	1.5	35.0	
8	Milk NaCl, 4 Gm.	141	89					
9	Milk NH_4Cl, 2 Gm.	133	73	42.7	7.57	1.4	41.3	V (i)
10	Milk NH_4Cl, 2 Gm.	138	94	31.8	7.48	1.3	30.5	V (f)
11	Milk 4 days after NH_4Cl	133	67	48.6	7.65	1.4	47.2	
12	Milk NaCl by clysis	136	69	48.6	7.66	1.3	47.3	VI (i)
13	Milk NaCl by clysis	135	81	35.0	7.62	1.1	33.9	VI (f)
14	Milk following NaCl by clysis	139	87	34.9	7.52	1.3	33.6	VII (i)
15	Milk following NaCl by clysis	138	84					VIII (i)
16	Milk following NaCl by clysis	135	81	41.5	7.62	1.2	40.3	VIII (f)

*Values for H_2CO_3 and $BHCO_3$ derived from the measurements of total CO_2 and pH.
†(i) and (f) indicate initial and final values for period.

The data from eight periods of study which were of from three to four days' duration are assembled in Table II. The values recorded are average per twenty-four hours for the periods. The measurements of Na and Cl in the stools display the consistently large excess of Cl; from two to three times the

*Parentheses are used in this paper as an abbreviation for "plasma concentration of . . . ."

Na content. In all of the periods the quantity of Cl entering the urine was barely measurable. As shown by the measurements of pH the stools were more acid than the urine, as would be expected from removal of Cl entirely by way of the intestinal tract. Urine pH, owing to absence of this large component of acid excretion, is sometimes above the pH of the plasma.

The obviously indicated attempt to raise the level of plasma (Cl) by providing an additional intake was carried out. It was found that with a daily intake of from 3 to 4 Gm. NaCl placed in the milk, plasma (Cl) was sustained at from 10 to 15 meq./L. above the level found for milk alone. This gain for

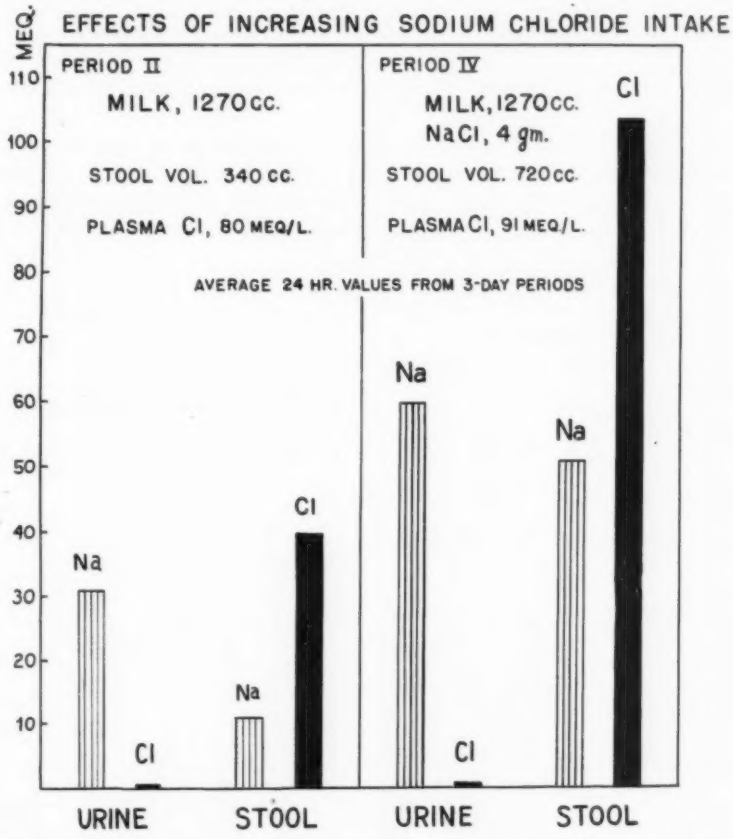

Fig. 3.—Showing the large increase in outgo of sodium and chloride in the stools and increase in stool volume when sodium chloride is added to the milk intake.

plasma (Cl) was, however, at the cost of a huge increase in the volume of the stools. The data given graphically in Fig. 3 are from periods II and IV (Table II) over which the daily milk intake was the same. During period IV and over a preceding period of several weeks, the milk contained 4 Gm. of added NaCl. Plasma (Cl) was found at 91 meq./L. as compared with 80 meq./L. for period II during which milk alone was given. The quite large stool volume found for this period was more than doubled when NaCl was added to the milk. An average daily stool volume of 720 c.c. is an exceptionally high mark for diarrhea in an infant.

TABLE II. VALUES PER TWENTY-FOUR HOURS FO

PERIOD	DAYS	REGIME	INTAKE Vol. c.c.	Na mM	Cl mM	K mM	N Gm.	STOOL Vol. c.c.	pH	Na mM	Cl mM
I	4	Similac	976	27.3	21.3	15.9	2.07	199		14.3	23.5
II	3	Milk	1,270	25.0	40.0	53.1	6.43	342	6.7	10.9	39.6
III	3	Milk, NaCl 3 Gm.[1]	1,307	62.7	78.4	54.6	6.45	482		36.6	68.8
IV	3	Milk, NaCl 4 Gm.[2]	1,270	94.0	109.0	53.1	6.43	720	6.2	50.7	103.3
V	3	Milk, NH_4Cl 2 Gm.	1,163	22.9	74.1	48.6	6.05	348		15.7	44.2
VI	4	Milk, NaCl 4.5 Gm. S.C.[3]	1,458	87.0	104.1	60.9	7.45	474	6.7	37.1	57.1
VII	4	Milk[4]	1,510	29.8	47.6	63.2	7.65	406	6.3	21.4	45.5
VIII	4	Milk[5]	1,123	22.3	35.5	47.1	5.58	310	6.6	19.0	36.5

[1, 2]The sodium chloride given in periods III and IV was placed in the milk.

[3]In period VI, sodium chloride was given by subcutaneous infusion of 500 c.c. of 0.9 per cent Na solution on second, third, and fourth days of the period.

Volume of daily intake, period VI, does not include salt solution given by clysis.

[4, 5]Periods VII and VIII immediately followed clyses of salt solution over a period of three days.

[6]In obtaining water balance, water of oxidation was computed on assumption of complete oxidati of fat and sugar intake. The insensible water loss was taken as 93 per cent of insensible weight l (Levine's factor).

The well-known effect of ammonium chloride of producing acidosis in a normal individual by increasing plasma (Cl) at the expense of bicarbonate suggested its suitability as an agent for reduction of alkalosis caused by recession of plasma (Cl). Accordingly, over period V, 2.0 Gm. NH_4Cl daily

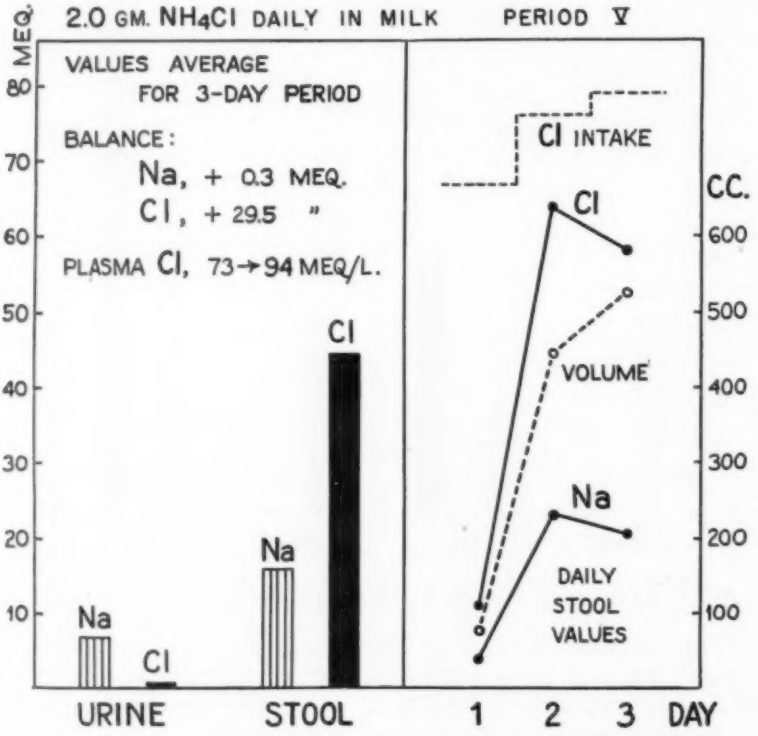

Fig. 4.—Effects of addition of ammonium chloride to the milk intake.

were given in the milk. A positive Cl balance of 29.5 meq. resulted (Table II) and plasma (Cl) was given a large lift; from 73 to 94 meq./L. (Table I). There was reduction of ($BHCO_3$) but curiously of only about one-half the extent of the (Cl) increase. From the day-by-day data for this period given

ENTY-FOUR HOURS FOR DATA FROM BALANCE PERIODS

STOOL Na mM	Cl mM	K mM	N Gm.	URINE Vol. c.c.	pH	Na mM	Cl mM	K mM	N Gm.	BALANCE Na mM	Cl mM	K mM	N Gm.	H_2O_e c.c.
14.3	23.5	6.6	0.37	151	6.4	6.9	0.3	10.1	1.55	+ 6.1	− 2.5	− 0.8	+0.14	− 65
10.8	39.6	16.4	1.05	364	7.3	20.9	0.3	36.4	4.73	− 6.7	+ 0.1	+ 0.3	+0.65	+155
36.6	68.8	20.2	0.52	215	7.7	32.1	0.8	24.7	5.06	− 6.0	+ 8.8	+ 9.7	+0.87	− 74
50.7	103.3	24.2	1.07	348	7.6	59.9	0.4	24.1	5.32	−16.6	+ 5.3	+ 4.9	+ 0.4	+ 76
15.7	44.2	26.3	0.55	160	5.7	6.9	0.4	12.5	3.80	+ 0.3	+29.5	+ 9.8	+1.70	+ 52
37.1	57.1	13.8	0.35	800	6.9	27.0	0.3	26.2	4.86	+22.9	+46.7	+20.9	+2.24	+239
21.4	45.5	21.4	0.38	543	7.2	11.7	0.5	41.0	5.54	− 3.3	+ 1.6	+ 0.8	+1.73	− 66
19.0	36.5	14.7	0.49	281	6.7	5.3	0.3	29.0	3.94	− 2.0	− 1.3	+ 3.4	+1.15	− 96

in Table III, it may be seen that the larger part of the Cl gain occurs on the first day of the period; on this day Cl retention was 84 per cent of intake. On the second and third days the greater part of intake is lost in the stools and there is a large increase in stool volume from an initial value which, for

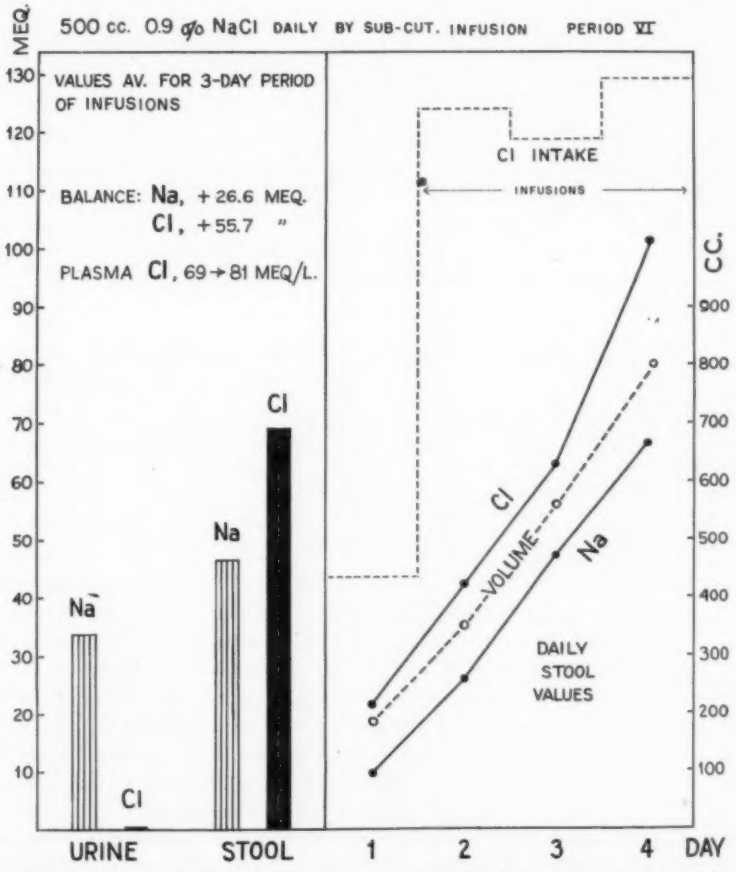

Fig. 5.—Effects of subcutaneous infusion of salt solution. Daily infusions were begun on second day of a four-day period of observation.

this infant, was unusually small. These features of the effects of NH_4Cl are shown again in Fig. 4. Daily stool volume is seen to rise with the large outgo of Cl. The data suggest that Cl removal in the stools will soon reach and perhaps overpass the level of intake. The daily supplement of NH_4Cl was con-

TABLE III. EFFECTS OF INGESTION OF 2.0 GM. AMMONIUM CHLORIDE DAILY

Day	INTAKE			STOOL				URINE				BALANCE	
	Vol. c.c.	Na meq.	Cl meq.	Vol. c.c.	pH	Na meq.	M meq.	Vol. c.c.	pH	Na meq.	Cl meq.	Na meq.	Cl meq.
1	935	18.4	66.9	74	6.5	3.3	10.7	158	5.9	5.9	0.2	+9.2	+56.0
2	1,235	24.3	76.4	445	7.6	23.3	64.0	223	5.6	9.1	0.7	−8.1	+11.7
3	1,320	26.0	79.1	525	7.6	20.6	58.0	100	5.7	5.6	0.3	−0.2	+20.8

tinued for five days beyond period V and 4 days later plasma (Cl) was found to have fallen to 67 meq./L. (plasma No. 11, Table I). Evidently a sustained elevation of plasma (Cl) cannot be expected from ingestion of this salt.

In order to observe effects of placing Cl behind the gastrointestinal tract, subcutaneous infusions of 500 c.c. of 0.9 per cent NaCl solution were given on three consecutive days. As recorded in Fig. 5, the infusions produced a large positive balance for Na and twice as large a gain for Cl, with the result that plasma (Cl) was raised from 69 to 81 meq./L. Even when given subcutaneously almost no Cl is removed in the urine and the greater part of sodium outgo is also in the stools. The day-by-day data for this period, including the day before infusions were begun, are given in Table IV. As shown by pH change, the increased removal of Na without Cl by the kidneys produced an intensely alkaline urine. Positive balance for both Na and for Cl declines extensively over the period of infusions; the largest gain being on the first day. The daily values for Na and Cl in the stools and for stool volume are shown in Fig. 5. Stool volume is seen to rise progressively and so extensively that on the last day of the period it reached the enormous value of 800 c.c. Chloride removal parallels stool volume and rapidly approaches the level of intake.

TABLE IV. EFFECTS OF INFUSIONS OF 0.9 PER CENT NaCl SOLUTION

Day	INTAKE				STOOL					URINE					BALANCE		
	Vol. c.c.	Na meq.	Cl meq.	K meq.	Vol. c.c.	pH	Na meq.	Cl meq.	K meq.	Vol. c.c.	pH	Na meq.	Cl meq.	K meq.	Na meq.	Cl meq.	K meq.
1	1,380	27.2	43.5	57.6	185	6.5	8.7	21.8	7.9	260	5.5	5.5	0.3	34.9	+13.0	+21.7	+14.8
2	1,480*	106.9	124.2	61.8	350	6.0	25.8	42.2	15.0	360	6.2	21.9	0.2	22.5	+59.2	+81.8	+24.3
3	1,320*	103.6	119.2	55.2	560	6.6	47.4	62.8	13 6	408	8.0	35.6	0.2	22.3	+20.6	+56.4	+19.3
4	1,650*	110.1	129.6	69.0	800	7.6	66.4	101.4	19.6	570	8.0	44.8	0.1	24.9	− 1.0	+28.2	+25.5

*Does not include 500 c.c. 0.9 per cent NaCl solution of subcutaneous infusion.

In order to observe the duration of gain from NaCl supplied by infusion, intake and outgo were measured over two periods, VII and VIII, with an interval of one day between them, directly following infusions of 0.9 per cent NaCl daily for three days as in period VI. Balance for both Na and Cl over the eight days covered by these two periods was approximately stationary (Table II). The gains from the series of infusions which preceded them, and which were presumably of the same order as found in period VI, were evidently well conserved. Plasma chloride fell gradually but not extensively (Table I). Stool volume was only slightly above the expected value for a milk intake without added NaCl. These data indicate that attempt to raise plasma (Cl) by infusions of NaCl solution at a minimal cost in diarrhea should consist in giving single infusions at intervals of several days. In period VI, the largest Cl gain and the smallest stool volume were found on the first day of the infusion period. Similar evidence regarding ingestion of additional Cl is provided by the data from the ammonium chloride period. It is probable that supplements of NaCl given intermittently would have produced elevation of plasma (Cl) of the same extent as was obtained by continuous administration

with much less increase in stool volume. Unfortunately this significance of the data was not recognized while the patient was under treatment. The measurements of nitrogen balance in Table I provide some evidence of nutritional improvement accompanying elevation of plasma (Cl) provided aggravation of diarrhea is avoided. When NaCl was given by infusion, period VI, and over the two periods, VII and VIII, following a series of infusions, satisfactory nitrogen balances were found. On a regime of continuous supplementation of NaCl intake which produced a greatly increased stool volume, nitrogen balance was, according to the measurements from period IV, barely positive. Without addition of NaCl to intake, period II, stool volume was approximately the same as for the periods, VII and VIII following infusions, but nitrogen gain was only one-half as large. These few measurements are slender evidence of benefit from NaCl. Whether related to the small elevation of plasma (Cl) or to the accompanying Na and water gains is not clear. It does not seem likely that nutritional improvement can be referred simply to repair of dehydration. This infant did not at any time present dehydration of clinically evident degree.

A negative balance for the intracellular base potassium was found only in the first period. There was, however, in the other periods a wide irregularity in the relation of potassium to nitrogen retention. The normal K:N ratio of cell fluid, expressed as K meq./N Gm. may be taken as 2.86. The ratios found for the positive balances of K and N for the individual periods are as follows: II, 0.5; III, 11.1; IV, 12.2; V, 5.8; VI, 9.3; VII, 0.5; VIII, 3.0. These data suggest an instability of either the volume of cell fluid or of its ionic composition which may well be of primary pathogenic significance.

SURMISE

Using this heading it may be permissible to set down briefly inferences which the measurements suggest.

The outgo of Cl in the stools cannot be explained by defective absorption. This is evident from the large positive balance found at the outset of a period of abruptly increased intake; for example, for the first day of the ammonium chloride period, retention was 84 per cent of intake indicating rapid absorption. The diarrhea is incidental to some disturbance of water and electrolyte control within the body which compels removal of chloride exclusively by way of the intestinal tract. This compulsory position of Cl outgo is clearly established by the absence of appreciable removal of Cl in urine when NaCl is supplied by infusion. The low plasma (Cl) cannot be explained by "loss" of Cl in the stools. As shown by the data in Table II, the Cl exchange, except for temporary gains produced by abrupt increase of intake, is approximately in balance. So there is no loss of Cl in the stools in the sense of ungoverned removal. The requirement for Cl removal in the stools produces the diarrhea and determines its degree. In approaching an explanation for the low plasma (Cl) it is significant that measures which ordinarily would raise (Cl) rapidly to its usual position are resisted. A small elevation can be sustained only under pressure of a large intake of Cl which is not quite offset by a greatly increased outgo in the stools; even so the margin is narrow and uncertain. These considerations produce the inference that the lowered position of (Cl) is part of a distortion of the physicochemical system of the body fluids and is not a primary event. Looked at in this way it is an adjustment imposed by an underlying defect. Of this the kidney is unaware and undertakes by limiting outgo in the urine to restore the usual plasma level. A lower position for

(Cl) can therefore be sustained only by regulated removal of Cl in the stools. The intestinal tract meets this requirement with surprising success, presumably by absorption from the lower bowel of chloride to a lesser extent than sodium from intake or, in the case of infusions of salt solution, from gastrointestinal secretions of normal composition carrying the administered sodium chloride into the bowel.*

Apparently the large extension of plasma bicarbonate is a consequence of the recession of (Cl). But there is the odd and perhaps significant circumstance that this increase of ($BHCO_3$) is not accompanied by the usual compensatory change in (H_2CO_3) in defense of pH. Continuing with the concept of preservation of a physicochemical system when under stress by distribution of distortion throughout its parts, the measurements in Table I suggest that the position of pH in the neighborhood of 7.6 may be a necessary adjustment. This surmise produces an astonishing implication; namely, that the extension of ($BHCO_3$) which brings pH to this unusual position commands the recession of (Cl). This would be an unusual attitude by ($BHCO_3$) which ordinarily alters its concentration willingly and nimbly in response to change in the concentrations of other ionic components of the plasma.

The measurements which have been presented provide no glimpse of the postulated initial defect in the ionic edifice of the body fluids which makes necessary the changes visible in the plasma; perhaps because it lies in the structure of intracellular fluid.

SUMMARY

Results of study of an infant exhibiting recession of plasma chloride, alkalosis, and a large excess of chloride over sodium in the stools are reported.

There was voluminous watery diarrhea which began at birth.

The findings indicate, but do not identify, an intrinsic defect in the control of electrolyte distribution in the body fluids.

We wish to acknowledge the invaluable assistance of Dr. Winthrop I. Franke and Captain Fred H. Allen, M.C., of the resident staff at the time of this study. The presence of alkalosis in the patient was first observed by Dr. Franke.

REFERENCE

1. Holt, L. E., Courtney, A. M., and Fales, H. L.: Am. J. Dis. Child. 10: 229, 1915.

*Obviously a differential absorption of sodium and chloride from the bowel might be postulated as the primary cause of the low plasma chloride. The author's interpretation of the evidence is against this view.

CONGENITAL ALKALOSIS WITH DIARRHEA

DANIEL C. DARROW, M.D.
NEW HAVEN, CONN.

THE following case is reported because it apparently represents an unrecognized syndrome exhibiting unusual disturbances in electrolyte metabolism. The patient came into the New Haven Hospital during a week when I visited Boston and heard James L. Gamble describe an almost identical case which he had investigated for about a year and the present studies were greatly aided by facts brought out by Gamble's work.[26] The characteristic feature is watery diarrhea leading to loss of more chloride than sodium in the stools. In the serum the concentration of chloride is extremely low and sodium somewhat low while the pH is extremely high. At times deficit of potassium develops and concentration of serum potassium is low. Gamble's case showed no lesions at autopsy that could explain the diarrhea. The case presumably represents a peculiar defect in the absorption of water, sodium, and chloride from the intestinal tract.

CASE HISTORY

The father and mother were healthy people of Italian extraction. They were aged 32 and 26 years when the patient was born. Three siblings, two older and one younger, were living and well. Familial diseases were not brought out by questioning.

The patient, a male infant, was born in another hospital on Oct. 26, 1941, after about "seven months'" gestation and weighed 2,350 Gm. The hospital records show that he lost 450 Gm. within forty-eight hours after birth and that he had loose stools during the first twenty-four hours. When the baby was six days old he was receiving clyses on account of the diarrhea. He was kept in the hospital for one month because of diarrhea and failure to gain in weight. When discharged he weighed 2,300 Gm.

The trouble noted at birth has continued up to the time of this report when the child was 2 years and 11 months old. According to the mother, he has never passed a normal, formed stool, and the number has varied from four to fourteen each day. This statement is substantiated by our observations during many months in the hospital. The stools, while he was receiving a milk diet, consisted of brown watery material mixed with yellowish solid material and looked like normal baby stools stirred into fine particles with a great deal of water. In a cylinder the solid material settled to the bottom leaving at least six times as great a layer of cloudy brown watery material. When solid food was given, the appearance was little altered except for the presence of vegetable fibers and green coloring matter. The actual diet has not otherwise affected the character of the stools. There was no evidence of painful peristalsis. The stools contained no pus, mucus, or blood and were not especially irritating to the skin since no unusual trouble was encountered despite almost continuous passage of these stools.

Before entry into the New Haven Hospital at the age of 9 months, the child's feeding was under the direction of a competent pediatrician and none of the formulas deviated greatly from accepted practice. Briefly, he received the following mixtures: (1) until 2 months old, Dextrigen with 10 per cent added dextrimaltose; (2) HY-PRO milk for two days; (3) from the eighth to the tenth week, milk containing 2 per cent fat and 10 per cent dextrimaltose; (4) from the third to fourth months, boiled, homogenized milk with added dextrimaltose. Orange juice was added during the second month but was given irregularly after the third month because the mother thought orange juice might aggravate the diarrhea. Oleum percomorphum was started at 2 months; Pablum at 2 months; vegetable purées at 4 months. The appetite was fairly good except during periods of exacerbation of the diarrhea leading to marked dehydration. Vomiting seldom occurred except during infections or during periods of marked dehydration.

At a time when the rest of the family was suffering from colds and when the baby was 9 months old (June 29, 1942), he developed fever, rhinorrhea, and rapid breathing. The

From the Department of Pediatrics, Yale University School of Medicine.

next day the pediatrician was called and found the temperature 102° F. During this day, there was vomiting and increase in the number of watery stools. Cough was evident on July 1 and on the following day the nasal discharge was more profuse. Another pediatrician was called on July 3 because the diarrhea was worse. He advised that the patient be treated in a hospital because of the alarming state of dehydration and prostration. Although this recommendation was refused at the time, the baby was brought to the hospital within twelve hours because he was so obviously becoming worse.

On admission to the New Haven Hospital, the baby was extremely dehydrated, undernourished and underdeveloped (age, 9 months; weight, 4,540 Gm.; head circumference, 40 cm.; chest, 37.5 cm.; length, 63 cm.). He was extremely restless and fretful, thrashing about with his hands and feet in an aimless manner. The eyes were sunken and the skin turgor poor. The mouth was dry; the tongue red with prominent papillae; the lips cracked and covered with yellow crusts. The nose showed a thin mucopurulent discharge, but the eardrums were essentially normal. The lungs and heart were normal except for tachycardia. The abdomen was prominent but not greatly distended. No signs of tetany were demonstrated. Without chemical examination of blood, he was given the usual treatment for diarrhea.

The temperature rose on the second day to 39.5° C. but was normal on the third day. With fasting, clyses of physiologic saline, infusions of 10 per cent glucose solutions and transfusions of blood, the baby improved remarkably, the weight increasing to 4,780 Gm. by the third day. Although the stools were still watery, they were less frequent. On this day food fortified with niacin, thiamine, and riboflavin was given and no more clyses administered until one was given on the sixth day in the hospital. On the tenth day when no clyses had been given for three days, he again showed extreme signs of dehydration; he had vomited twice, the stools were frequent and watery, and the temperature rose to 40° C. The next day (July 15) the blood serum showed marked increase in concentration of bicarbonate and decrease in chloride (Table I). In addition to fasting and intravenous injections of glucose

TABLE I. SERUM CONCENTRATIONS PER LITER

DATE	HCO_3 mM	Cl mM	Prot. Gm.	Na mM	K mM	pH	pCO_2 mm Hg	THERAPY
7/15/42	34	61	80	138		7.73	34	None for 5 days
7/17/42	14	92	62	147		7.52	18	Intensive saline clyses, 2 days
8/ 4/42	39	54		118	1.5	7.72	32	No therapy for 4 days
10/ 6/42	33	64	70	139	3.8	7.57	39	KCl + NaCl, 1 Gm. each*
1/16/43	39	69		131	5.6	7.57	47	NaCl, 1 Gm.*
1/22/43	47	45		136	2.4	7.46	74	None for 2 days
12/14/43	27	94	66	136	4.3	7.34	52	NaCl, 2 Gm.*
12/24/43	38	58		125	4.8	7.61	44	Fever, refusal of food 2 days
1/ 5/44	35	82		139	4.1			NaCl 3 and KCl 1 Gm.*
4/25/44	28	84	74	132	5.4	7.45	44	NaCl 3 and KCl 1 Gm.*

*For seven days or more.

and plasma, the baby received 500 c.c. of physiologic saline on both July 15 and 16. On the morning of July 17, the serum bicarbonate was low and serum chloride almost normal. However, the pH was high. On August 4 (32 days in the hospital) the serum showed high bicarbonate and low chloride. At this time he had received no clyses for four days and had not vomited recently. Although the baby had been diagnosed a usual type of diarrhea on admission, the findings on this date assured the diagnosis of alkalosis dependent on loss of chloride in excess of sodium in the stools and any influence of vomiting could be excluded.

The subsequent course will be briefly summarized. He was in the hospital from the thirty-seventh to eighty-fourth week of life; during the ninety-second week when he became dehydrated owing to lack of salt intake during an attack of mild measles; from the one hundred and third to one hundred and twelfth week when he was in the hospital for experimental studies; from the one hundred and fourteenth to one hundred and thirty-second week for treatment and study. In the hospital he required almost daily clyses of physiologic saline for six weeks, but thereafter he received from 1 to 3 Gm. of NaCl and 1 Gm. of KCl added to the milk and he gained slowly. The sodium chloride was apparently essential and the potassium chloride usually beneficial although he did well at times without KCl. Other substances did not apparently influence the diarrhea nor well-being. Apple pectin, citrous pectin, aluminum hydroxide, and KH_2PO_4 were tried based on the observations of Dennis and Visscher[1] who suggested that dibasic anions promote the absorption of chloride although they delay the absorption of water. The stools never became normal though several times at home and once in the hospital they were a little less watery and frequent for one or two

weeks (from one to three a day instead of from seven to fourteeen). He has always drunk a great deal of fluid, the intake being from 150 to 200 c.c. per kilogram of body weight from the ninth to the twenty-eighth month of life.

While under observation the boy suffered from one attack of pneumococcal pneumonia, one severe infection with type B influenza bacillus, several colds, and grippe. Except for loss of appetite and consequent decrease in salt intake, he showed remarkable resistance to infections, and, if the dehydration was treated, recovery from infections seemed as satisfactory as in normal children.

His progress may be judged by the slow gain in weight (aged 52 weeks, 5.5 kg.; 75 weeks, 6.5 kg.; 100 weeks, 8.9 kg.; 125 weeks, 10.5 kg.). At 2 years and 11 months, he weighed 11.3 kg. and measured 88 cm. in length and 47.5 cm. in head circumference. During the first months of life he was so sick that his activity was limited, but later he felt fairly well and enjoyed life. He walked at 23 months. At first he everted his feet at almost a right angle, but this position was due to sleeping on his stomach with his feet everted, and the use of the feet in walking has gradually become normal. He learned to talk late but at 27 months used four-word sentences and understood simple commands. He learned to use the toilet for stools at about the age of 2½ years.

Psychometric and psychologic examinations by Drs. Gesell and Amatruda were made at 12, 23, and 29 months. The suggested developmental quotient of the first examination was 57, but this was not considered to have prognostic significance on account of the severe physiologic handicap up to this age. The other examinations suggest an intelligence or developmental quotient of 80 to 88. His personality is outgoing and friendly, enabling him to adjust well to the hospital and people. He is quite distractable and does not show continued interest and drive in his play.

Tetany was seldom manifest despite profound alkalosis. He had a convulsion probably due to alkalotic tetany which is described in the protocol for the third metabolic period. Occasionally he showed carpal spasm; only once did he have a good Chvostek sign; laryngeal crow was never heard.

Intestinal juice was analysed for pH, Cl, Na, and K as obtained by a Miller-Abbott tube. On Nov. 5, 1942, the tube was allowed to descend overnight and was found in the jejunum by x-ray. Selected analyses are shown in Table II, the order of the sampling being from the lower intestinal tract to the stomach.

TABLE II. COMPOSITION OF INTESTINAL JUICE (NOV. 5, 1942)

SPECIMEN NO.	TUBE LENGTH CM.	pH	Cl mM/L.	Na mM/L.	K mM/L.	PROBABLE POSITION
1	183	5.20	77	66	25.0	Jejunum*
2	167	5.02	120	141	8.3	
3	152	6.73	123	146	7.6	
6	107	6.76	134	141	7.0	
8	76	6.87	124			
10	51	6.88	119			
12	30	7.14	112			
15	18	7.25	124	139	6.4	Duodenum
16	14	5.45	87		15.0	Stomach

*X-ray.

The first sample was acid and had a chloride concentration greater than that of sodium and a fairly high potassium concentration. The resemblance of this sample to the stools is brought out in Table III. The other samples are essentially normal including sample 16 of gastric juice. Passing the Miller-Abbott tube at a later date did not show a jejunal sample with higher chloride than sodium. The study indicates that there was a tendency for the concentration of the intestinal juice to assume the pattern of the patient's stools with respect to Cl, Na, and K. The change was probably gradual and only became manifest in the jejunum or lower. The colon was probably involved since in the morning

TABLE III. RATIOS OF Cl:Na:K

		Cl	Na	K
Sample I*	Jejunal	1	0.85	0.32
Balance 1	Stool	1	0.62	1.62
Balance 2	Stool	1	0.37	0.18
Balance 3	Stool	1	0.42	0.17
Balance 4	Stool	1	0.49	0.17

*Taken from Table II.

he often passed large watery stools which probably had been present in the colon for some time.

A gastrointestinal series following a swallow of barium was obtained Aug. 24, 1942. The small intestines revealed hypomotility since the barium meal first reached the cecum after six hours. The jejunal loops showed definite evidence of abnormality characterized by considerable coarsening of the mucosa, marginal fraying and irregularity, slight dilatation, and suggestive segmentation. At five and six hours the bulk of the barium lay in the ileal loops; at nine hours, in the ascending colon. The colon showed marked hypermotility. The barium enema showed a relative lack of haustral markings. The x-ray diagnosis was atypical pattern of the small intestine and a question of ulcerative colitis.

Sigmoidoscopic examination on Sept. 9, 1942, was difficult because of continual descent of watery feces. No abnormalities of the mucosa were noted.

Cerebrospinal fluid and venous serum were obtained under mineral oil at the same time. The concentrations per kilogram of water are shown in Table IV.

TABLE IV. COMPARISON OF CEREBROSPINAL FLUID AND VENOUS SERUM*

	pH	pCO_2 Hg mm.	Sugar mg. %	H_2O %	Per kg. H_2O					
					HCO_3 mM	Cl mM	Na mM	K mM	Ca mM	P mM
C.S.F.†	7.40	52	60	99	29.3	112.0	133.5	4.75	1.02	0.52
Serum	7.43	62	72	92	39.7	91.3	137.5	7.07	2.99	1.30

*May 6, 1943.
†Cerebrospinal fluid.

The spinal fluid differs from a filtrate of plasma in that the carbon dioxide tension is lower, the concentration of chloride is higher and the concentration of bicarbonate, lower. The data indicate that the usual relationship between the concentration of electrolyte of the serum and spinal fluid was maintained. This finding is of interest because it shows that alkalosis and low chloride do not affect the peculiarities of the blood-brain barrier.

Representative serum analyses are given in Table I. Note the following: (1) The extremely high pH measured with a glass electrode giving normal values with normal blood. The extremely high values were measured at 38° C. and there is no reason to doubt their validity. With improvement, almost normal values were obtained. (2) The extremely low chloride values were repeatedly confirmed. Only during periods of improvement were values over 80 mM per liter obtained even during periods when the diet contained added chloride. (3) The high bicarbonate concentrations accompanied the low concentrations of chloride and only approached normal on a few occasions. (4) Low sodium concentrations were the rule, but only once was an extremely low value found. (5) Many serum potassiums were low when the diarrhea was producing extreme changes. At other times the values were normal. (6) Serum phosphorus was sometimes low (2.2 mg. per cent) but usually normal (3.9 to 4.7 mg. per cent). (7) Nonprotein nitrogen, sugar, serum protein, and calcium were normal (two determinations of Ca, 11.5 mg. per 100 c.c.).

BALANCE EXPERIMENTS

Four balance experiments were carried out which show slightly different features. The data are shown in Tables V, VI, VII, and VIII and in the supplementary protocols. Each balance is for three days except for an additional day in the fourth study. Electrolyte is expressed in millimoles in the tables.

TABLE V. FIRST METABOLIC PERIOD (THREE DAYS)

	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	Mg mM	H_2O c.c.	Solids Gm.
Intake	8.57	46.5	37.7	73.5	52.0	53.8	0.94	1,660*	299.0
Urine	3.05	0.0	4.7	7.6	1.1	0.3	0.30	400	5.5
Stool	2.40	78.5	49.3	127.5	26.4	36.2	0.53	750	20.0†
Output	5.45	78.5	54.0	137.1	27.5	36.5	0.83	1,150	
Balance	3.11	-32.0	-16.3	-61.7	24.5	17.3	0.11	510	

*1,735 c.c. milk + 224 c.c. water.
†Including 2.6 Gm. fat.
Initial body weight 4,790; final, 4,700 Gm.

TABLE VI. SECOND METABOLIC PERIOD (THREE DAYS)

	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	H_2O c.c.	Solids Gm.
Intake	10.7	78.0	46.8	111.6	65.0	67.0	2,028*	372
Urine	0.83	0.0	15.1	91.8	26.1		725	10.7
Stool	2.0	106.3	39.6	19.0	37.9	57.8	661	27.2
Output	2.83	106.3	54.7	110.8	64.0	57.8	1,386	
Balance	7.87	-28.2	-7.9	0.8	1.0	9.2	642	

*2,160 c.c. milk + 240 c.c. water.
Initial body weight 5,040; final, 5,000 Gm.

TABLE VII. THIRD METABOLIC PERIOD (THREE DAYS)

	N Gm.	Cl mM	Na mM	K mM	P mM	H_2O c.c.	Solids	pH
Food	11.5	234	188	106	54	2,720*	360	
Urine I	1.58	0.0	7.3	0.94	5.7	125		8.15
II	1.41	0.0	13.9	0.93	3.8	100		8.42
III	1.31	0.0	8.1	1.67	4.75	120		8.17
Total urine	4.30	0.0	29.3	3.54	14.25	345		
Stool I	0.70	75.8	32.6	13.9	7.34	650		5.85
II	0.47	56.0	21.7	8.68	2.21	410		6.04
III	0.18	16.3	7.7	2.59	0.56	135		6.51
Total stool	1.35	148.1	62.0	25.17	10.11	1,540	30	
Total urine + stool	5.65	148.1	91.3	28.7	24.36	1,885		
Balance	5.85	86	96.8	77.3	29.64	1,195		

*1,800 c.c. of milk + 630 c.c. of water + 650 c.c. of subcutaneous saline.
Initial body weight, 6,160; final, 6,400.

TABLE VIII

	N Gm.	Cl mM	Na mM	K mM	P mM	Ca mM	H_2O c.c.	Solids Gm.
				Fourth Metabolic Period (3 days)				
Food	9.92	153	158	41	59	56	2,630*	380
Urine	8.30	0.0	60.2	51.2	36		560	30
Stools	1.65	159	81.6	28.0	29	40	955	23
Output	9.95	159	141.8	79.1	65		1,515	
Balance	-0.03	-6	16.2	-38.1	-5.8	16	1,115	
				Fourth Metabolic Period (1 day)				
Food	2.8	45	41.9	15	17.2	16.0	765†	110
Urine	0.5	0.0	11.7	11.2	5.4		137	3
Stools	0.62	62.5	27.3	9.5	5.1	9.5	427	10
Output	1.12	62.5	39.0	20.7	10.5		564	
Balance	1.68	-17.5	-2.9	-5.7	6.7	6.5	201	

*1,910 c.c. of milk mixture + 1,100 c.c. of water.
†555 c.c. of milk mixture + 320 c.c. of water + 14 mM $Al(OH)_3$.
Initial body weight, 8,600 Gm; third day, 8,430 Gm; final day 8,200 Gm.

For reasons brought out in the supplementary protocols the characteristic features of the different balance periods are as follows:

First Balance Period: The changes in body electrolyte which occurred during development of a very severe degree of depletion of tissue electrolyte.

Second Balance Period: The changes in body electrolyte which occurred when a less severe grade of depletion of tissue electrolyte developed. Presumably the administration of KCl before and during the period explains the different reaction.

Third Balance Period: The changes in body electrolyte which occurred during treatment and partial recovery from severe depletion of tissue electrolyte. Both NaCl and KCl were used in the treatment.

Fourth Balance Period: The changes in body electrolyte which occurred during development of severe depletion of tissue electrolyte. The interesting feature is the loss of body chloride and gain in body sodium.

SUPPLEMENTARY DATA ON BALANCE PERIODS

The collections of urine in all experiments were for the period of time without resort to catheterization. In the first two experiments, the stools were likewise collected over the stated time. This procedure did not involve a great error since stools were passed very frequently. Carmine stool markers were used for the last two periods. Analyses were done in duplicate on urine, stools, and food. Blood was collected before and after the periods. Owing to the limited amount available, serum proteins could not always be estimated. The chemical methods were adaptations of standard methods used in this laboratory.[4]

First Metabolic Period.—The first metabolic period of three days ended on Aug. 14, 1942. The food was cow's milk with 2 per cent fat and 10 per cent added dextrimaltose. On the successive days 650, 630, and (estimated) 475 c.c. were taken. No parenteral fluid was given during the collection, but 224 c.c. of water were drunk.

The collections were made while the child was changing from a fairly good condition to one of marked dehydration. One week before the period the body weight was 4.82; at the onset, 4.79; at the end, 4.70 kg. A hypodermoclysis of 200 c.c. of physiologic saline was given one day before the period but not on the preceding two days. At the onset he was afebrile but developed temperatures of 38.8 and 39° C. on the second and third days. He vomited part of the last two feedings. During the collections he developed signs and symptoms of dehydration (loss of skin turgor, sunken eyes, restlessness, and tachycardia). After the period, a single hypodermoclysis produced prompt recovery.

Second Metabolic Period.—The second metabolic period of three days ended Sept. 4, 1942. The food was the same as that of the first period except that 0.5 Gm. of KCl was added to each day's mixture. Each day 720 c.c. of food were taken and there was no vomiting. No parenteral fluid was given, but 240 c.c. of water was drunk.

The collections were made while the boy was developing moderate dehydration, but the condition was better at the beginning and end of the period than at the corresponding times of the first period. He received the same food containing added KCl for one week preceding the collections; he received hypodermoclyses of 200 c.c. of physiologic saline on the three days preceding the period. One week before the period the body weight was 5.06; at the beginning, 5.04; and at the end, 5.00 kg. The temperature rose to 39° C. on the last day.

Third Metabolic Period.—The third metabolic period of three days ended Jan. 30, 1943. The daily urines and stools as collected for the period of time were analyzed separately but the stools were marked off for the three days by carmine. The diet was 600 c.c. of whole milk with 60 Gm. of sucrose and 1 Gm. each of KCl and NaCl. All the diet was taken together with 620 c.c. of water. In addition, hypodermoclyses of 250, 200, and 200 c.c. of physiologic saline were given on the successive days.

The collections were made during recovery from severe dehydration. On a diet containing 2 Gm. of NaCl the boy had been doing well without clyses for nine weeks. On January 20, he weighed 6.25 kg. but became dehydrated and required a clysis on January 22 because the salt had been inadvertently omitted from the diet on January 20. On January 23, 24, and 25, he received daily clyses and the weight increased to 6.48 kg. During the day which preceded the metabolic period, extra salt was omitted from the diet and no clyses were given. The weight decreased to 6.16 kg. and marked signs of dehydration developed on the first day of the metabolic period. The temperature rose to 39° C.; five hours after

starting the collection he had a convulsion. He stopped sucking from a bottle, became rigid, opisthotonic with clenched fists, ceased breathing, and became cyanotic for about two minutes. There were twitchings of the face and a few clonic movements of the legs. After breathing 5 per cent carbon dioxide in oxygen for a few minutes, he relaxed and regained consciousness. The hypodermoclysis of saline was given at this time. Despite absence of Chvostek and Trouseau signs, the convulsion was regarded as due to alkalotic tetany. No further trouble was encountered and by the end of the period the boy was in good condition. The final weight was 6.40 kg.

Fourth Metabolic Period.—The fourth metabolic period ended Oct. 21, 1943, after four days. It had been planned to have a control period of three days followed by a period of three additional days with added aluminum hydroxide, but this was impossible because the boy became too sick and dehydrated. The stools of the first three days and final day were demarkated with carmine. The food was 800 c.c. of whole milk containing 80 Gm. of dextrimaltose and 3 Gm. of NaCl. On the last day, 30 Gm. of Amphojel* were added. This contains 2.03 Gm. or 30 mM of aluminum hydroxide. The study is reported as one period of three days and one period of one day. However, the data are discussed as a single period of four days.

The study was made during the development of marked dehydration and signs and symptoms of tetany. During the summer he did well at home with no extra salt according to the parents. It was discovered later that he ate large amounts of spaghetti with salty sauce. When he came into the hospital on Oct. 16, 1943, his weight decreased from 8.88 to 8.50 kg. by October 18 because no salt was added to the diet. With 2 Gm. of salt added to the milk at this time, he seemed to be doing well at the onset of the metabolic period on October 21. The body weights of the successive days of the period were 8.60, 8.57, 8.33, and 8.20 kg. He gradually developed signs of dehydration during the collections; there was no fever but on the final day there were positive Chvostek and Trouseau signs.

TABLE IX. STOOL CONTENT PER DAY

DATA FROM HOLT, COURTNEY, AND FALES[2]				BALANCE PERIOD OF PATIENT				
	NORMAL	LOOSE	WATERY	1	2	3	4	4
Water Gm.	36	133	293	250	220	516	318	427
Dried weight Gm.	9	13	21	7	9	10	8	10
Fat Gm.	3	4	8	0.8				
N Gm.	0.3	0.6	0.9	0.8	0.7	0.5	0.8	0.3
Cl mM	0.6	4.0	8.0	26	35	49	53	62
P mM	3	3	3	9	13	3	10	5
Na	1.3	5.5	11.6	16	13	31	27	27
K	3.8	7.7	17.5	42	6	8	9	10
Ca	12	13	10	12	19		13	10

The metabolic handicap of the child is revealed in the stools. Table IX shows the daily output in the stools in comparison to data published by Holt, Courtney, and Fales.[2] These authors divided the stools into normal, loose, and very loose so that the comparison of the values of the very loose stools with those of our patient gives a basis for evaluating the peculiarities of this diarrhea when compared to cholera infantum. The difference in water content is probably not so great as not to be accounted for by the greater size of our patient at the time of the last two analyses. However, the chloride output is four or more times as great and the sodium output from one to two and one-half times as great. In the first balance period the potassium is likewise about three times as great but in the other periods potassium excretion in the stools is comparable. The comparison suggests defective absorption of chloride as the principal difference from the usual type of infantile diarrhea of severe grade.

It will be noticed that the defective intestinal absorption explains the chemical findings in the serum. Although stool water is from two to four and one-half times that of the urine, there is little tendency to the development of a rise in nonprotein nitrogen. In all periods, stool chloride is greater than stool sodium while urine chloride was not detected and urine sodium was low. Stool

*John Wyeth & Brother, Inc., Philadelphia, Pa.

pH was acid while urine pH was alkaline. These results for pH were repeatedly confirmed at other times. The alkalosis is dependent on the greater loss of chloride than sodium. That the kidney did not maintain normal serum concentration is due to the magnitude of the stool losses of sodium and chloride.

DISTRIBUTION OF BODY WATER AND ELECTROLYTE DURING BALANCES

Present knowledge of the factors controlling the distribution of body water and electrolyte is sufficiently well-established to permit an interpretation of the electrolyte balances. Although the theoretic background is largely based on analyses of tissues of dogs, cats, and rats,[3, 4, 5, 6, 7] the same factors apply to human beings. Briefly it is known that, although some chloride is intracellular, the amount is small in comparison to extracellular chloride. On the other hand, while sodium is chiefly an extracellular ion, there are considerable quantities in bones as an integral part of the calcified matrix[8] and in the intracellular phase of skeletal muscle and probably in the intracellular phase of other tissues.[7] In the present experiments, the balances of calcium are too small to affect significantly the sodium metabolism. On the other hand, the data show unmistakable evidence of variations in intracellular sodium and potassium, and for this reason calculations will be applied which demonstrate these changes.

Briefly two chief assumptions are made: (1) that all chloride remains extracellular and that the changes in serum chloride concentration and the balance of chloride measure the changes in extracellular water and (2) that the volume of extracellular water is 25 per cent of the body weight when the patient is not dehydrated. Since the balances of chloride are large, these assumptions are sufficiently accurate to justify the calculations.

Using brackets [ ] for concentrations and parentheses ( ) for amounts, the following equations are self-explanatory:

[Initial serum Cl] (Initial extracellular H_2O = (Initial extracellular Cl)
(Initial extracellular Cl) + (Balance Cl) = (Final extracellular Cl)
(Final extracellular Cl) ÷ [Final serum Cl] = (Final extracellular H_2O)
[Initial serum Na] (Initial extracellular H_2O) = (Initial extracellular Na)
[Final serum Na] (Final extracellular H_2O) = (Final extracellular Na)
(Final extracellular Na) - (Initial extracellular Na) = (Balance extracellular Na)
(Balance Na) - (Balance extracellular Na) = (Balance intracellular Na)

In the equations serum chloride was multiplied by 1.11 to approximate that of a serum filtrate; serum sodium, by 1.02. These are average corrections for serum water and the Donnan effect. Analogous equations were used to calculate changes in extracellular potassium. In the tables a corrected value is given for the balance of cellular K. This was obtained by multiplying the balance of nitrogen by 3 since about 3 mM of potassium are associated with 1 Gm. of muscle nitrogen.[5, 6] Presumably retention of nitrogen will demand this much retention of potassium to produce normal tissues. The changes in total body water are assumed to be equal to the changes in body weight. From the calculated change in extracellular water, the balance of intracellular water was obtained. The results of these calculations are shown in Table XI.

In Experiment 1, despite the development of clinical dehydration, the total loss of body water is small as indicated by the decrease in body weight of only 90 Gm., but the loss of extracellular water is 380 Gm. as calculated from the serum chloride concentrations and the chloride balance (Tables V, X, XI). Sodium was not lost in amounts comparable to the loss of chloride, but large

amounts of potassium were excreted in the stools. The calculated shift of sodium into the cells is approximately equal to the calculated deficit of intracellular potassium (Table XI).

TABLE X. SERUM DATA FOR BALANCE EXPERIMENTS

DATE	PERIOD	BODY WEIGHT kg.	CONCENTRATION PER LITER HCO_3 mM	Cl mM	Prot. Gm.	Na mM	K mM	pH
8/11/42	1A	4.79	35	61		138		
8/14/42	1B	4.70	47	55		124		7.49
9/ 1/42	2A	5.04	41	68	65	132	4.0	7.65
9/ 4/42	2B	5.00	45	59		132	2.7	7.57
1/27/43	3A	6.16	45	51		129	2.2	7.59
1/30/43	3B	6.40	35	69		138	4.5	7.56
10/21/43	4A	8.60	38	50		130	4.6	7.59
10/25/43	4B	8.20	46	46	70	130	1.7	7.57

TABLE XI. CALCULATED DISTRIBUTION OF WATER AND ELECTROLYTE

PERIOD	TIME	EXTRACELLULAR H_2O kg.	Cl mM	Na mM	K mM	INTRACELLULAR BALANCE H_2O kg.	Na mM	K mM	K* mM	N Gm.
1	Initial	1.20	82	169						
1	Final	0.82	50	103		0.27	50	-60	-69	3.11
2	Initial	1.26	95	170	5.0					
2	Final	1.03	67	139	2.8	0.19	23	1.4	-22	7.87
3	Initial	0.78	45	103	1.7					
3	Final	1.70	131	240	7.6	-0.68	-40	71	54	5.85
4	Initial	2.10	117	278	9.6					
4	Final	1.84	94	244	3.1	-0.14	47	-50	-37	1.65

*Corrected for balance of nitrogen ($-N \times 3$).

In Experiment 2, the loss of chloride is almost as great as in Experiment 1, but the loss of sodium is appreciably less and change in body potassium negligible. These results again indicate loss of extracellular water greater than loss of total body water (230 Gm. as compared to 40 Gm. of weight loss). The evidence of shift of sodium into the cells is again found, but the deficit of intracellular potassium is indicated only by the positive balance of nitrogen at a time when total body potassium remains unchanged. The calculated shift of extracellular sodium into the cells is equal to the calculated deficit of intracellular potassium (Tables VI, X, XI).

In Experiment 3, body weight increased about 240 Gm. while extracellular water increased almost a kilogram. This increase in extracellular water is indicated by a large retention of chloride. The retention of sodium alone is not sufficient to account for this much expansion of extracellular fluid. Retention of potassium without nitrogen is, however, sufficient to account for enough shift of sodium from the cells to expand extracellular sodium sufficiently to account for the concentration of sodium in serum at the end of period 3 (Tables VII and XI).

Attention is directed to the fact that in Experiment 3 the daily loss of water and electrolyte in the stools diminishes as the deficits of body chloride, sodium, and potassium are replaced. The loss in the stools of water, chloride, sodium, and potassium on the third day is less than the daily average of any of the other periods and this finding contrasts sharply with the greater loss of water, sodium, and chloride on the first day than that of the daily average in the other experiments. Only potassium in Experiment 1 is lost in greater amounts than on the initial day of Experiment 3. The evidence is clear that absorption is better when body deficits are restored. On clinical grounds this

finding was repeatedly confirmed by the fact that after severe electrolyte loss was produced either by withdrawing salt or by the disturbances accompanying infections, the diarrhea became worse and considerable therapy with NaCl and KCl was necessary before the child could again function as well as he did before the severe electrolyte loss had developed.

Experiment 4 is like Experiment 1 in that severe clinical dehydration developed. The loss of weight (400 Gm.) is more than sufficient to account for the loss of extracellular water (260 Gm.). The interesting feature is a positive balance of sodium at a time when there is a negative balance of chloride. Loss of extracellular sodium is indicated by the calculated shift of sodium into the cells accompanied by a corresponding loss of intracellular potassium (Tables VIII and XI). The shift of sodium into cells is over two times the positive balance of sodium. If this had not been the case, the boy would probably have developed an intolerably high concentration of serum bicarbonate.

DISCUSSION

The exact nature of the defect of this child must remain a matter of speculation. Gamble informs me that in their case, the autopsy revealed no abnormality of the gastrointestinal tract either grossly or microscopically that would explain the chemical findings. Reduplication of the intestinal tract with functioning gastric mucosa seems, therefore, to be excluded. Visscher and his collaborators[2] have shown that the absorption of sodium and chloride in the small intestine is intimately associated with transfer of water. However, the fluid leaving the gut contains more sodium and chloride than that remaining, so that the fluid in the gut becomes hypotonic with respect to plasma at the same time that it decreases in volume. Furthermore, there is transfer of fluid containing salt and water to the gut from plasma. In the presence of certain divalent anions such as sulfate, chloride enters the blood more rapidly but water more slowly. Aluminum hydroxide has a similar effect. These processes cannot be the result of purely osmotic forces such as those involved in the absorption of salt solutions from subcutaneous tissues. Expenditure of energy in doing work against a concentration gradient is, therefore, involved in absorption of water and salt from the intestinal tract and such processes require cellular activity and presumably enzymes.

In the patient one of the metabolic activities is apparently defective in the intestines, but the defect does not involve directly other functions of the gastrointestinal tract since absorption of nitrogen, phosphorus, calcium, fat, and, by indirect inference, carbohydrate are essentially normal and the composition of the intestinal juice in the upper intestinal tract is normal with respect to pH, chloride, sodium, and potassium. One analysis of jejunal juice was acid and contained chloride in excess of sodium. The defect seems to be a general one involving absorption of water, sodium, and chloride from the small and large intestines. Since colonectomized patients get along better than this patient, the small intestines as well as the colon seem to be involved in this severe and peculiar dysfunction. This hypothesis is suggested by the single sample of jejunal juice containing more chloride than sodium and a relatively high concentration of potassium. Perhaps one cannot rule out a perverted function of the colon which modifies a normal ileal juice so as to produce the composition illustrated by the stool analyses.

None of the usual diarrheal diseases lead to a similar picture of alkalosis due to loss of chloride in excess of sodium in the stools. Although Dr. Fuller Albright has told me personally about a case of ulcerative colitis in an adult

who showed similar serum findings and excessive loss of chloride in the stools, these findings have not been reported in typical ulcerative colitis. While the usual infantile types of diarrhea probably have defects in the absorption of water and salts from the gastrointestinal tract, increased peristalsis is probably a more important factor. The reverse is probably true in this patient as suggested by the gastrointestinal series.

In addition to illustrating deficit of sodium and chloride as a cause of the clinical picture of dehydration, the patient shows clearly the substitution of sodium for potassium within the cells. If we assume that muscle accounts for all the calculated shifts of sodium and potassium and that muscle represents about 0.4 of the body weight, intracellular potassium was replaced by sodium in amounts approximating 10 mM per 100 Gm. of fat-free solids both at the end of Balance 1 and the beginning of Balance 3. This is about 25 mM per kilogram of fresh muscle and equivalent to from one-fifth to one-fourth of muscle potassium or from five to eight times the usual intracellular sodium. The data do not prove that the exchange does not involve other tissues as well as muscle, but experimental work on animals points to muscle as the chief site of this type of exchange and muscle is the only tissue with sufficient bulk to account for such large shifts of sodium and potassium.

Tissue analyses have repeatedly shown that sodium may replace potassium within muscle cells. Normally, muscle potassium in rats varies from 44 to 48 mM per 100 Gm. of fat-free solids and this variation of potassium may occur without serious disturbance in the well-being or perceptible change in intracellular sodium.[6] Similar variations apparently can be obtained in dogs and cats.[9, 10] Decrease in muscle potassium below the normal range has involved replacement with about an equivalent amount of sodium in the studies that have so far been made.[6, 12, 13, 14] The exchange may amount to about one-half the usual content of potassium. Conditions leading to this abnormal composition of muscle thus involve the development of a deficit of body potassium. Replacement of muscle potassium by sodium was first demonstrated in rats receiving diets low in potassium.[6, 12] Since the stool always contains some potassium and the kidneys are unable to excrete urine free of potassium, deficit of potassium gradually develops on low potassium diets and is reflected in a low concentration of this ion in serum as well as muscle. On normal diets deficit of potassium may be produced by repeated injections of desoxycorticosterone acetate,[6, 14, 26] cortical hormone,[17] estrogens[15] and testosterone.[15] Two papers [18, 19] give evidence that deficit of potassium sometimes develops in Cushing's syndrome probably owing to hyperadrenalism. Thus, certain hormones alter the urinary excretion of potassium and produce low concentrations of potassium in both serum and muscle. One of the patients studied by Stewart and Rourke[20] (case of R. H.) retained sodium in excess of chloride and lost potassium in excess of nitrogen so as to indicate exchange of potassium for sodium in muscle. This patient was an essentially normal woman receiving large amounts of solutions of glucose and salt intravenously after a gynecological operation. The relative excess of the loss of potassium over nitrogen reported by Atchley and associates,[21] suggests that during the development of diabetic acidosis, deficit of potassium may be produced. Owing to the lack of a suitable method of estimating sodium, relative retention of sodium cannot be proved by the data. Some of the experimental animals studied by Elkington and Winkler[11] show similar phenomena. Thus the literature contains considerable evidence that diuresis in general may occasionally produce a deficit of body potassium and the phenomenon of loss of potassium and retention of sodium in muscle is probably fairly frequent. Harri-

son, Tompsett, and Barr[22] described two cases of sprue with low concentrations of serum potassium and probable deficit of muscle potassium since weakness was relieved by ingestion of potassium salts. In their patients the loss of potassium was accounted for by the bulky stools. In all these conditions, deficit of muscle potassium was produced by excessive loss in relation to the intake.

Talbot, Butler, and MacLachlan[23] found low serum potassium and disproportionately large retention of nitrogen in relation to potassium in a patient receiving testosterone. The data suggest that deficit of potassium may develop during rapid storage of nitrogen although the experiments are complicated by previous administration of desoxycorticosterone acetate.

The present case fits in with the observations that deficit of muscle potassium is accompanied by loss of body potassium, but certain observations require further comment. Unpublished data from this laboratory as well as older analyses[2] indicate that stool potassium is below 5 mM per day, probably 1 to 3 mM in infants. The first experiment shows extremely high stool potassium which suggests that the character of the diarrhea is directly the cause of the change in the tissue potassium. In the second period, however, stool potassium is about one-sixth that of the first experiment despite almost equal water output. In the second period large amounts of potassium were found in the urine despite evidence of developing potassium deficit as shown by nitrogen retention. In the fourth period similar urinary output of potassium leads to deficit of potassium despite relatively small stool potassium. Thus, deficit of potassium developed owing (1) to excessive loss of potassium in the stools, (2) to excessive urinary excretion at a time when nitrogen was stored, and (3) to excessive urinary excretion during a period with a positive sodium balance. These facts suggest that alkalosis may be the primary cause leading to the deficit of muscle potassium and the excessive intracellular retention of sodium. The observations indicate that alkalosis so alters the equilibrium between plasma and muscle cells that the intracellular phase assumes a composition low in potassium and high in sodium. Yannet[24] found no change in muscle potassium of cats subjected to alkalosis for about twenty-four hours. However, in similar experiments in rats lasting from four to seven days, I have found definite increase of intracellular sodium and decrease in potassium. Thus the composition of the intracellular phase of muscle is dependent on the state of equilibrium with extracellular fluids as well as gross deficits produced by excessive loss of potassium.

There is, in the literature, some suggestive evidence that the deficit of muscle potassium and high intracellular sodium tends to be accompanied by alkalosis of the serum. McQuarrie, Johnson, and Ziegler[18] and Willson, Power and Kepler[19] have called attention to cases of Cushing's syndrome which show decreased concentration of serum chloride and potassium and increased concentration of sodium and bicarbonate. Return to normal serum electrolyte patterns could be produced by administration of potassium salts but not by ammonium chloride or sodium chloride. Similar serum electrolyte pictures probably accompany repeated injections of desoxycorticosterone acetate and low potassium diets.[6, 13, 14] Bicarbonate has not been directly estimated in the published studies, but low concentration of chloride and normal or high concentrations of sodium in these experimental animals indicate that serum bicarbonate is probably high. This suggests that deficit of potassium secondary to loss of this ion tends to induce low chloride and high bicarbonate concentrations in serum.

The only striking difference between our observations and those of Gamble are the increased volume of stools which Gamble found when sodium chloride was added to the food. In Gamble's case the average stool concentrations of

Cl, Na, and K were 122, 61, and 45 mM per liter; in ours, 136, 62, and 23. (The latter set of values excludes the exceptionally high K of our first balance period.) Thus the composition of the stools was much the same. His metabolic periods illustrate the same type of exchange of sodium for potassium, but the exchange is not so nearly equivalent during the metabolic periods. This discrepancy may be explained either by a relative lack of potassium in the cells or in the food which would make such an equivalence difficult to attain. At no time was KCl administered to Gamble's patient, while our patient received KCl before all metabolic periods except the first. Furthermore, KCl was given during the second and third periods. It is probable that Gamble's patient suffered at all times from a variable degree of potassium deficit. It seems likely that correction of severe alkalosis by administration of sodium chloride cannot be entirely successful as long as deficit of potassium persists. Such an hypothesis may account for the difference in reaction of the two cases to treatment with sodium chloride.

The data bring out evidence that loss of chloride alone leads to diminution of extracellular water and increase in intracellular water. The change in extracellular water involves a shift of extracellular sodium into the cells where it replaces an equivalent amount of potassium. This process leaves total body water relatively constant. In none of the experiments is the balance of water predicted by the balance of univalent base or the change in concentration of sodium. The change in distribution of body water accompanying loss of chloride in excess of sodium resembles the state described following loss of extracellular electrolyte without change in total body water,[25] but loss of potassium produces loss of extracellular sodium by permitting sodium to enter the cells.

Ferrebee and associates[14] described muscular weakness in dogs developing deficits of muscle potassium. While the patient was weak during the periods of deficit of body potassium, nothing resembling true paralysis was observed. However, correction of deficit of body potassium by administration of potassium chloride was obviously beneficial.

In the treatment of potassium deficit, potassium chloride is logically the salt to use since deficit of chloride may be as great as the deficit of potassium and the chloride will be needed either to expand extracellular fluids on the release of intracellular sodium or to neutralize sodium in the urine if sodium is destined to be excreted.

Heart injury is known to be produced by deficit of body potassium.[17] Clinical symptoms, x-rays, and electrocardiographs did not reveal abnormalities of the heart in this patient.

SUMMARY

A report is made of a new syndrome. The patient showed intractable watery diarrhea from birth to the age of 2 years, 11 months (the time of this report). The stools were acid, contained considerable amounts of sodium, chloride and, at times, potassium. The alkaline urine contained no chloride, little sodium, and variable amounts of potassium. Stool chloride was always greater than stool sodium and stool water greater than urine water. Absorption of nitrogen, fat, carbohydrate, phosphorus, and calcium were essentially normal. As a result of these disturbances, the boy grew slowly, and was subject to frequent exacerbations of the diarrhea accompanied by signs and symptoms of dehydration. The blood serum showed extreme alkalosis, the maximal changes being pH 7.73; bicarbonate, 47 mM per liter; chloride 45 mM per liter; sodium, 118 mM per liter. Occasionally, serum potassium was low (1.5 mM per liter)

but usually normal. Usually no signs of tetany were present but tetanic convulsions occurred once and carpopedal spasm, occasionally.

Metabolic data are presented which show that as chloride is lost more rapidly than sodium, extracellular sodium is transferred into intracellular fluids and approximately equivalent amounts of potassium are released from the cells and excreted. Similarly when dehydration is treated with sodium chloride and potassium chloride, insufficient sodium is retained to account for the expansion of extracellular chloride but retention of potassium accounts for the release of sufficient sodium from cells to replace the deficit of extracellular sodium and to explain the changes in concentration of extracellular electrolytes.

The alkalosis and low serum chloride are accompanied by no evidence of change in the blood-brain barrier.

The displacement of muscle potassium by sodium is discussed.

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PERSISTING LIVER DAMAGE FOLLOWING CATARRHAL JAUNDICE

GEORGE W. SALMON, M.D., HOUSTON, TEXAS, AND
ELLEN EHRENFEST RICHMAN, M.S., ST. LOUIS, MO.

ONE of the aspects of the problem of catarrhal jaundice that is receiving an increasing amount of attention is the question of the existence of persisting liver damage following apparent clinical recovery. A brief survey of recent reports on this aspect of catarrhal jaundice indicates that it may not be the benign disease it is usually considered. Kalk[1] in 1932, Soffer and Paulson[2] in 1934, and Kornberg[3] in 1942 studied a total of fifty-seven patients who had recovered from an attack of catarrhal jaundice from four months to fifty years previously. They reported that thirty-six of these patients gave evidence of persisting impairment of liver function as shown by the bilirubin excretion test. Hurst and Simpson[4] in 1934 reported their inability to demonstrate the existence of hepatic insufficiency by means of the levulose tolerance test in patients who gave a history of having had a typical attack of catarrhal jaundice some years previously. McLeod[5] in 1944 reported having performed galactose tolerance tests on ten patients with jaundice seen during an epidemic in an institution for the feebleminded. All of the tests were positive. Four of these patients were rechecked one year later and all still showed some impairment of liver function. Altschule and Gilligan[6] in 1944 reported a study of thirty-six patients who had recovered from an attack of catarrhal jaundice from one to twenty-nine years previously. They found hyperbilirubinemia in 25 per cent.

It has been our purpose to follow cases of catarrhal jaundice during the attack and into the convalescent period with two of the newer liver function tests to ascertain the presence or absence of persisting liver damage. The first of these tests is the cephalin-cholesterol flocculation test of Hanger.[11] This is a serologic reaction found in the presence of parenchymal liver disease probably due to some alteration affecting the gamma globulin.[7] The second is the decrease in the diastatic activity of the serum. This is a purely empirical observation for which there is as yet no adequate explanation.[8] Bromsulfalein dye tests and intravenous hippuric acid tests were performed on some of the patients and the results have been included.

MATERIAL

The sixteen cases included in this report were selected from almost thirty cases seen by us at the St. Louis City Hospital during the past two and one-half years. The basis for selection was, first, confidence in the accuracy of the diagnosis and, second, adequacy of follow-up observations.

The question of exactly what catarrhal jaundice is and whether or not it may represent a group of diseases we do not attempt to answer. What the term means to us is best explained by this brief clinical description of the cases reported here.

The jaundice was usually mild and rarely of more than three weeks' duration. Nausea was almost a constant symptom and vomiting was usually present. Epigastric discomfort was a frequent complaint and abdominal pain was present in one-half of the cases. Diarrhea was occasionally present. Fever was

From the Department of Pediatrics and the Snoderas Laboratory of the St. Louis City Hospital, and the Department of Pediatrics of the Washington University School of Medicine.

usually present but it rarely exceeded 39° C. The liver was almost always slightly enlarged and tender. Although several patients gave a history of having had clay-colored stools, in no instance was this observed during the hospital stay. Two of the patients gave a history of a preceding upper respiratory infection. The blood count showed no constant significant alteration. The white cell count varied from five to eighteen thousand. Monocytosis was occasionally present and in one instance reached 34 per cent. The disease seemed to be one essentially of the first half of life. In our experience the degree of icterus did not necessarily coincide with the clinical severity.

We have made no effort to subdivide or classify our cases into infectious jaundice, "true" catarrhal jaundice, epidemic jaundice, benign hepatitis, jaundice with or without gastrointestinal episodes, and so forth, as is sometimes done. No case with a history of having ingested or been in any way exposed to any substance that might possibly cause jaundice was included. No case of jaundice seen concomitantly with a disease such as malaria or pneumonia was included except one (J. R.) where jaundice accompanied Flexner dysentery. That Flexner dysentery and infectious jaundice may have some relationship has been pointed out by Thorne and Estabrook.[9] In only one instance was there more than one case in a household (J. T. male and J. T. female were brother and sister). There was an interval of one month between the two attacks. Four of the patients were members of the hospital personnel. One intern (A. H.) had the disease in December, 1942; a second intern (W. G.), in January, 1943; a nurse (R. C.), in March, 1943, and a third intern (J. Y.), in July, 1943. Some of the patients may actually have had mild attacks of Weil's disease. None of them received laboratory examinations for this disorder.

METHODS

The icterus index was performed according to Davis' modification[10] but on venous blood.

The cephalin-cholesterol flocculation test was performed as outlined by Hanger.[11] The emulsion used was a partially oxidized type.* Emulsions were prepared freshly on the day used. Controls were performed. The tests were set up within a few hours of the time of obtaining the blood and read at twenty-four and forty-eight hours. As will be outlined later in this paper we consider the twenty-four-hour reading of more significance and have not included the forty-eight-hour result in this report. The tests were read as either negative or positive. If positive, an effort was made to estimate the extent of flocculation by use of the terms 1, 2, 3, and 4 plus.

The diastatic activity of the serum was estimated by the amyloclastic method of Somogyi.[12] On the recommendation of Gray and associates[8] we have considered values of between 80 and 150 as a normal range, values of between 60 and 80 as borderline, and values of below 60 as definitely subnormal. On the graphs, however, we have included all values below 75.

The bromsulfalein dye test was performed as outlined by Rosenthal and White.[13] Two milligrams of dye per kilogram of body weight were injected intravenously and a blood specimen taken after an interval of twenty minutes. When using this dose of the dye we have considered the complete disappearance of the dye from the blood after an interval of twenty minutes as a normal standard. We base this practice on the reports of MacDonald[14] and Mateer

*Supplied to us through the courtesy of Dr. David Klein of the Wilson Laboratories, Chicago, Ill.

and associates[15, 16] and have ourselves[17] shown this interval of time to be preferable even in small infants.

The intravenous hippuric acid test was performed as outlined by Quick.[18] The amount injected was 1.77 Gm. of sodium benzoate (equivalent to 1.5 Gm. of benzoic acid) dissolved in 20 c.c. of distilled water. The interval of time for collection of urine was one hour. The urine was analyzed for hippuric acid by the method of Weichselbaum and Probstein.[19] We have considered 1.0 Gm. of hippuric acid as the minimal normal amount to appear in the urine in one hour.[18] This is equivalent to 0.68 Gm. of benzoic acid or 0.8 Gm. of sodium benzoate. The results appearing on the graphs have been *calculated as sodium benzoate.*

RESULTS

The results of our investigation have been graphed in Figs. 1 to 4. The graphs have been so arranged that as normal values for the various tests are obtained the abscissa is approached.

Cephalin-Cholesterol Flocculation Test.—Cephalin-cholesterol flocculation tests were obtained in all of the sixteen cases. In fifteen of the cases the test remained positive for a much longer period of time than was required for the icterus index to return to normal. The period of time required for the test to become negative varied from three weeks (A. K.) to about seven months (P. M.) after the return of the icterus index to normal. In the one exception (A. H.) the test during the height of the icterus index was never more than 2 plus and became negative fully three weeks before the icterus index returned to normal.

During the period of observation following the subsidence of the jaundice the patients were free of any subjective or objective manifestations suggestive of hepatic insufficiency. Any patients who during this period contracted another illness which might possibly have altered the results obtained with this test were eliminated from the series and were not included in this report.

Our results showing the cephalin-cholesterol flocculation test persisting to be positive following an attack of catarrhal jaundice is at variance with other reports. These, in general, indicate that the degree of positivity of the test parallels the clinical course.[20, 21, 22, 23, 24] The remarkable consistency of our results, however, lends support to their value.

Our only criticism of the cephalin-cholesterol flocculation test has been the occasional finding of positive tests in apparently healthy normal individuals and the frequent finding of positive tests in patients suffering from some illness in which it was difficult to postulate liver damage. Others seem to have encountered the same problem.[15, 21, 22, 24, 25, 26] This has been attributed to variations of sensitivity of testing emulsions.[16, 22, 25] Some have attempted to solve this problem by disregarding one plus reactions.[15, 26, 27] Our approach to this problem has been to consider the twenty-four-hour reading as of more significance.

Serum Diastase.—Serum diastase determinations were obtained in fifteen of the sixteen cases and in one of the fifteen (R. C.) there were no observations during the period of jaundice. There are, therefore, fourteen cases for analysis.

From the graphs it is apparent that in only one instance (J. L.) did this test fail to show values of below 75. In seven of the fourteen cases [J. T. (male), P. S., L. H., E. M., B. D., J. T. (female), P. M.] results of this test were approximately parallel to the icterus index, although the last four mentioned showed an unexplained secondary fall during the period following the

return of the icterus index to normal. In six of the fourteen cases (J. R., A. K., H. A., W. G., J. Y., and A. H.) values of below 75 were seen during the period of jaundice and did not rise to 75 or above in a much longer period of time than was required for the icterus index to return to normal. Actually in five of these six cases the diastase values did not return to 75 or above during the

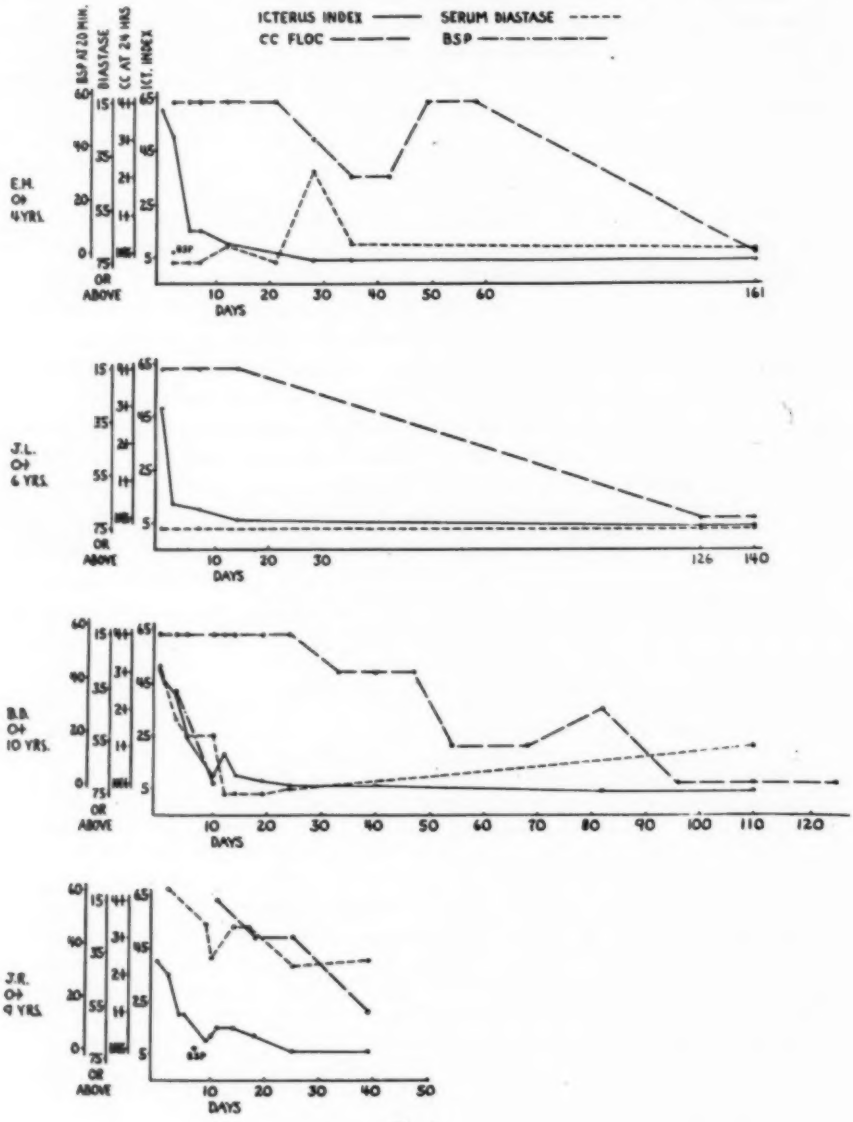

Fig. 1.

period of observation which ranged from 14 days (J. R.) to 217 days (H. A.) following the return of the icterus index to normal.

If the fourteen cases are reanalyzed as to whether or not values of below 60 were obtained, the results do not differ significantly from those we have outlined, since but two other cases would be eliminated. In the first of these

(E. M.) the serum diastase fell to 69 during the period of jaundice but had a marked secondary fall to 41 as the icterus index returned to normal. The second (P. S.) was a mild case in which the serum diastase at the peak of the icterus index fell to 68.

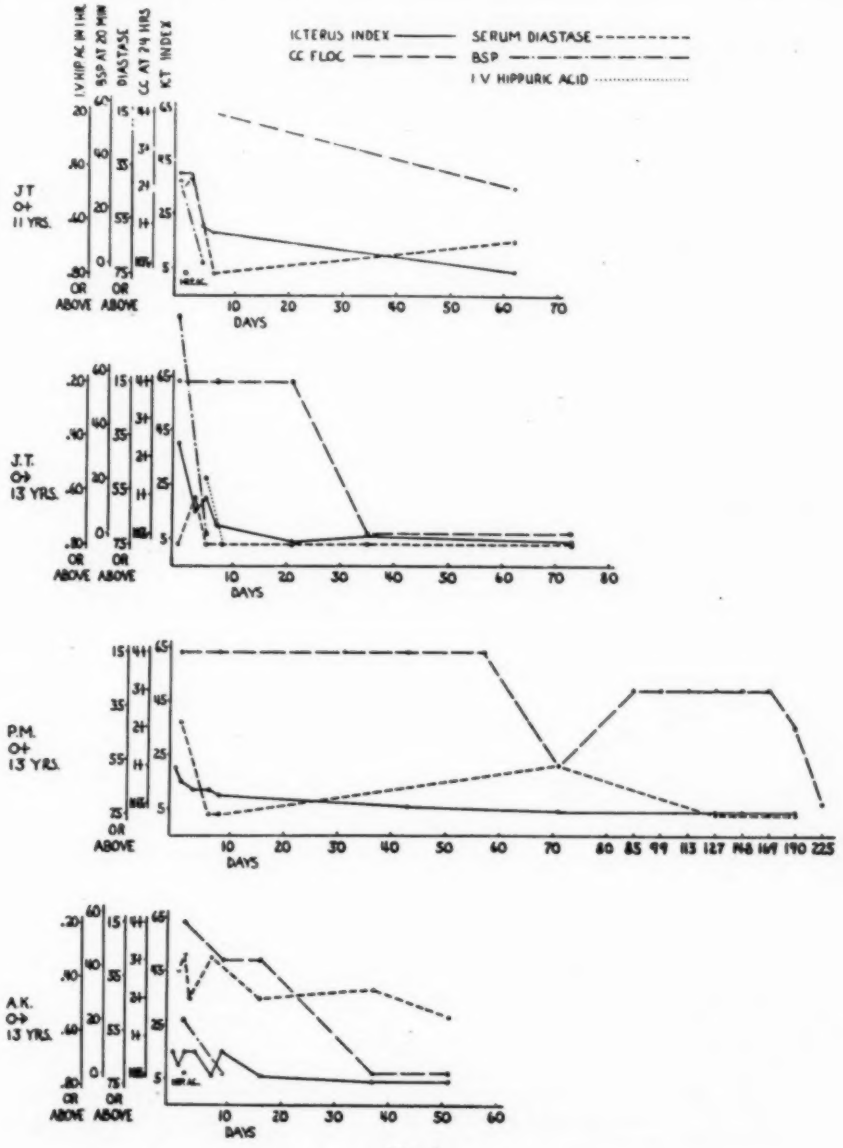

Fig. 2.

During the period of observation following the subsidence of the jaundice the patients were free of any subjective or objective manifestations suggestive of hepatic insufficiency. Any cases which during this period contracted another illness which might possibly have altered the results obtained with this test[8, 28] were eliminated from the series and were not included in this report.

Bromsulfalein Dye Test.—Bromsulfalein dye tests were obtained in nine of the sixteen cases. Six of these nine cases [B. D., J. T. (female), J. T. (male), A. K., P. S., and H. A.] had two tests each. The first test was obtained during the peak and the second during the decline of the icterus index. Similar results were obtained in each instance. Abnormal results were obtained at the time of

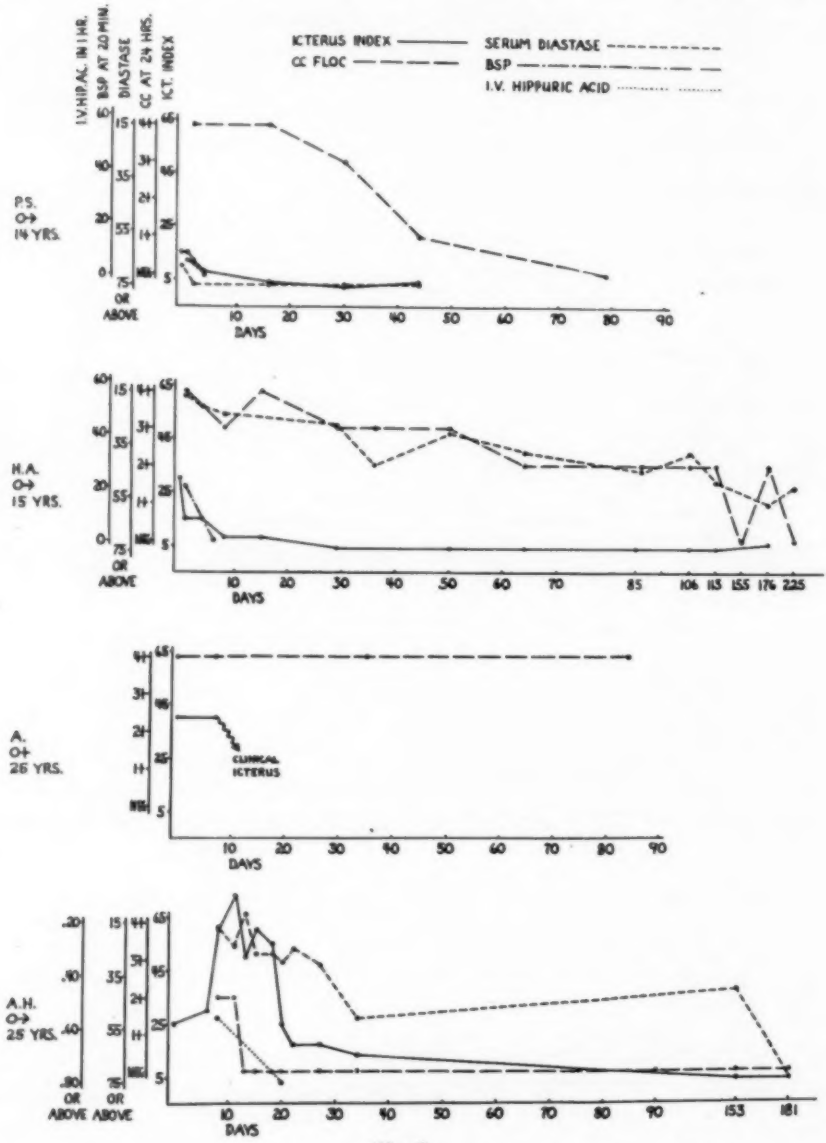

Fig. 3.

the first test and the degree of abnormality was roughly in proportion to the height of the icterus index. Normal results were obtained at the time of the second test.

Three of these nine patients had but one test each. One of the patients (L. H.) had an abnormal test during the peak of the icterus index and the test

was not repeated. One of the patients (J. R.) was not tested during the peak of the icterus index but had a normal test more than ten days before the icterus index returned to normal. One of the patients (E. M.) had a normal test during the peak of the icterus index.

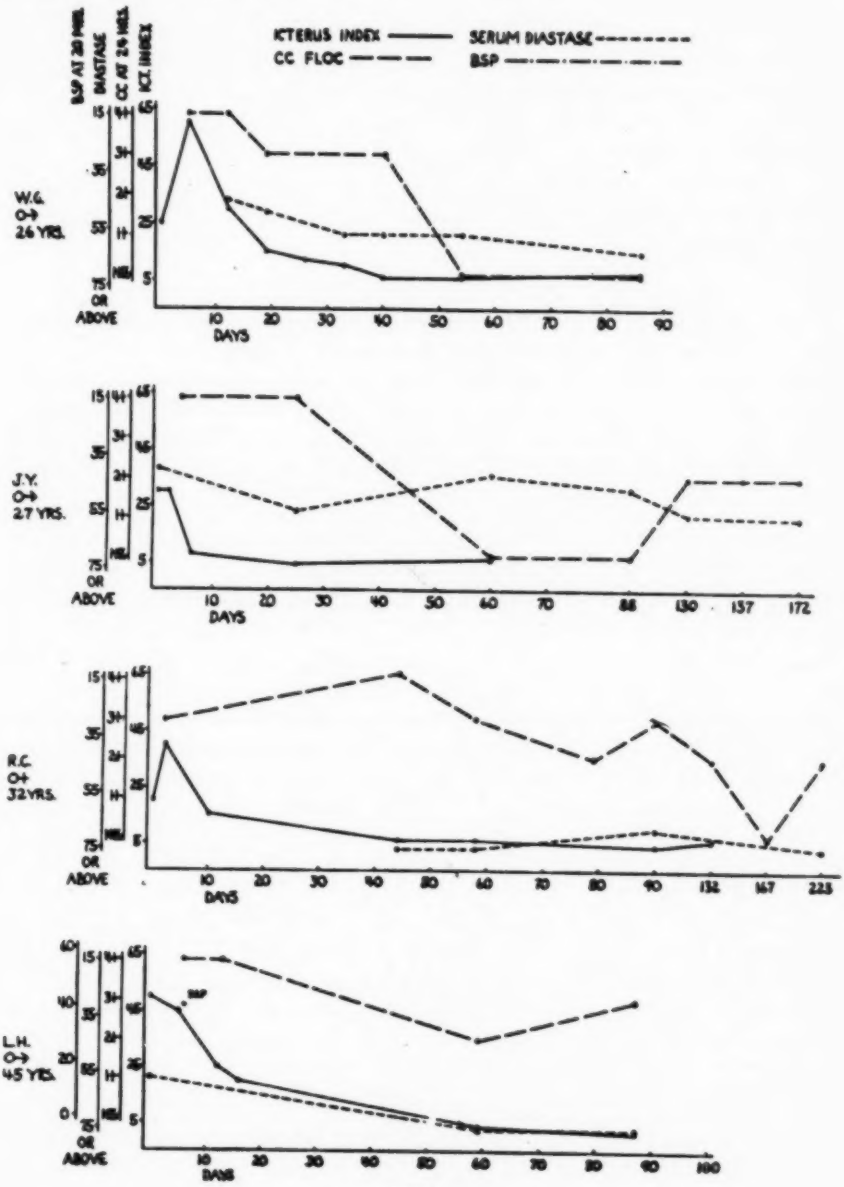

Fig. 4.

From our results in these few cases it is apparent that results obtained with the bromsulfalein dye test were approximately parallel to the icterus index.

Intravenous Hippuric Acid Test.—Intravenous hippuric acid tests were obtained in four of the sixteen cases. Because of the difficulty in obtaining ac-

curately timed urine specimens we have found this test to be of limited value in small children. Unfortunately, the test was not obtained in a high proportion of members of the older age group. Three of the patients [J. T. (female), J. T. (male), and A. H.] had two tests each. The first test was obtained during the peak and the second during the decline of the icterus index. Similar results were obtained in each instance. Abnormal results were obtained at the time of the first test and the degree of abnormality was roughly in proportion to the height of the icterus index. Normal results were obtained at the time of the second test. One of the patients (A. K.) had a normal test during the peak of the icterus index, but this was a mild case.

From our results in these few cases it is apparent that results obtained with the intravenous hippuric acid test were approximately parallel to the icterus index.

DISCUSSION

In our experience the degree of icterus has not necessarily coincided with the severity of the other manifestations of catarrhal jaundice. Even though the degree of icterus may not necessarily be the most accurate manifestation of the severity of the disease, it is, after all, the most distinctive manifestation and one which is easily measured. These are the reasons why of all the manifestations of catarrhal jaundice we chose the icterus index as the one manifestation with which to compare the results of our tests.

Although neither the mechanism of the cephalin-cholesterol flocculation test nor the reason for the lowering of the diastatic activity of the serum in the presence of liver damage is well understood, current medical literature indicates that they are being more and more accepted as liver function tests.

CONCLUSION

Liver damage, demonstrable by the cephalin-cholesterol flocculation test and the lowering of the diastatic activity of the serum, may persist for a period of a few weeks to several months following apparent clinical recovery from an attack of catarrhal jaundice.

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HOSPITAL MORBIDITY AND MORTALITY OF INFANTILE ECZEMA

A Report of One Hundred Consecutive Hospitalized Cases of Infantile Eczema Without Deaths

Stephan Epstein, M.D.
Marshfield, Wis.

With the Assistance of Sister M. Luitgardis, Record Librarian

THE occurrence of severe complications and even death among infants hospitalized because of infantile eczema has led to repeated warnings that children with eczema should not be admitted to a hospital, but should be taken care of at home or at a foster home. However, this is not always possible or practical, especially in severe generalized eczema. Such cases are quite common in rural districts; they are frequently due to sensitivities to environmental factors such as cattle dander. In these instances management at home is very difficult or even impossible.

From Jan. 1, 1937, to June 30, 1944, one hundred cases of infantile eczema were hospitalized at St. Joseph's Hospital, Marshfield, Wis. No deaths occurred among these children. The following is a report of this series with a discussion of causes of hospital morbidity and mortality of infantile eczema.

PRESENTATION OF CASES

This report covers all infants with eczema up to 2 years of age. The term eczema is used here in the broader sense as it is commonly applied.[22] Eczema in infants can rather readily be grouped clinically in four groups:

1. *Atopic dermatitis.*—Atopic dermatitis is the most common form of eczema in children. It begins early in life, frequently between the second and fourth month. It is characterized by a more or less acute, itching dermatitis. Practically always the face is involved but frequently it extends to arms, legs, and body. The child may be covered with scratch marks. Other manifestations of atopy may be present.

2. *Seborrheic Dermatitis.*—Seborrheic dermatitis often appears during the first few weeks of life with the well-known scaly eruption of the scalp commonly called "cradle cap." Later lesions appear on the face and body. Typical cases are characterized by sharply outlined, erythematous, scaly lesions, without pruritus. Combinations of atopic and seborrheic dermatitis are not infrequent.

3. *Contact Dermatitis (Epidermitis).*—In infants contact dermatitis is usually manifested by an acute or subacute dermatitis of relatively short duration. As a rule, it is not symmetrical and relatively rarely involves the face.

From St. Joseph's Hospital and the Marshfield Clinic.

It is most common on the legs and buttocks but may affect any part of the body. In this group are included those cases of dermatitis that clinically resemble epidermitis without definite proof that they are contact dermatitis.

4. *Infectious Eczema (Chiefly That Form Called Intertrigo).*—Intertrigo is manifested by eroded, usually more or less sharply outlined patches of eczema in the folds along the neck, axillae, and groins. It is apparently a form of infectious eczema, partly of bacterial origin (streptococcus or other bacteria), partly of fungus nature (monilia or other yeastlike fungi). Heat and moisture and the ensuing maceration are important contributing factors.

In order to permit comparison with previous reports the eczema cases are here presented in table form similar to those of Koch and Schwartz,[1] Glaser and Edwards,[2] and Schwartzman and associates.[3] Every admission was counted as a new case. There was a total of one hundred admissions, fifty-eight male and forty-two female. Two infants were admitted twice; and one, three times. Tables I and II present the eczema cases grouped according to the classification we have presented. The cases of atopic dermatitis (1 to 78) are reported separately in Table I.* All other eczemas (79 to 100) are given in Table II. Table III presents a control group.

INCIDENCE OF MORBIDITY (COMPLICATIONS)

A total of twenty-three complications (in twenty-one infants) was recorded, making the incidence for the whole series of one hundred cases twenty-three per cent. Of the sixty-four infants admitted with uncomplicated eczema, fifteen (23.4 per cent) developed complications. Of the thirty-six infants who presented complications on admission, six (16.6 per cent) acquired additional complications. The difference of the rate of complications between these two groups is of no significance.

There is, however, an important difference between the atopic and nonatopic children. Table IV shows that all complications but one occurred among the infants with atopic dermatitis.

NATURE OF COMPLICATIONS

Table V lists the nature of complications developed by the children with infantile eczema.

The complications contracted at the hospital were nearly all infections of the respiratory or gastrointestinal tract. The situation in regard to complications present upon admission is entirely different (Table VI).

Table VI shows that skin infections were common in both the atopic and nonatopic groups. But of the respiratory and gastrointestinal complications again all but one were observed among the atopic children. There was nothing particular about the various complications from which the infants with eczema suffered except three instances of that peculiar smallpoxlike eruption which is now generally called Kaposi's varicelliform eruption. This is quite an alarming complication and deserves more attention than it has had. The three cases, therefore, shall be briefly reported. The disease has been discussed recently by several authors (Barton and Brunsting,[4] Lynch,[5] Wenner[6]).

*Table I shows that atopic dermatitis, either alone or combined with seborrheic dermatitis, accounts for more than three-quarters of all the eczemas in this series. In general, atopic dermatitis is the most common form of infantile eczema. It would appear even more so in a group of hospitalized babies, because the other forms of eczema less frequently require hospitalization.

Kaposi's varicelliform eruption is similar in some respects to variola or vaccinia and is characterized by a constitutional reaction of unusual severity. On top of a pre-existing dermatitis, usually atopic dermatitis of infants, but also of adults, a vaccinia like eruption appears rather rapidly. The patient shows signs of a severe infection with high fever. Clinically we find the typical depressed vesiculopapular lesions of vaccinia, either singular or confluent. The whole face may be involved and turn into a swollen, eroded mass. This condition resembles eczema vaccinatum. However, the latter is a different condition. Eczema vaccinatum is generalized vaccinia in eczema patients who either have been vaccinated themselves or have come in contact with vaccinated persons. Kaposi's varicelliform eruption, as recent investigations have demonstrated, is a severe infection due to the virus of herpes simplex.[4, 5, 6]

In my three cases, Kaposi's eruption was superimposed on atopic dermatitis.

CASE 1 (Table I, Case 20).—J. G., 16 months of age, was admitted March 11, 1941. Eczema of face and arms had been present for the past fourteen months. One week prior to admission, the mother had noticed a papular eruption on the face which turned into pustules two days later. At the same time fever was noticed. The child appeared ill. Two days after the onset, the patient appeared rather stuporous. The lesions on the face became worse and new lesions appeared on the face and wrists. Neither the child nor anyone in the family had been recently vaccinated. Upon admission the child presented the typical picture of a weeping infantile eczema covered with numerous, smallpoxlike pustules. There was marked enlargement of upper cervical glands and a purulent discharge from the right ear. The temperature was 104° F. The secondary infection, under sulfonamide treatment, showed rapid improvement. The temperature went down to 100° F. after twenty-four hours. Uneventful recovery followed.

CASE 2 (Table I, Case 49).—K. O'D., 7 months of age, was admitted June 19, 1943. The eczema had started at the age of 10 days and had gradually become worse. About two weeks prior to admission pustular lesions had appeared on the face. On admission the child presented a severe eczema of face, arms, and legs. The lesions were covered with numerous pustules, many of them having a smallpoxlike appearance. The whole left side of the face was eroded and turned into one crusted and purulent mass. The general condition was relatively good. The next day the temperature rose to 105° F.; the child appeared seriously ill. In spite of treatment with sulfathiazole, the high fever continued until June 22. On that day sulfadiazine was instituted in the afternoon. The child began to improve; the temperature subsequently did not go over 100° F. Recovery was rapid. Later a partial paralysis of one foot developed which the attending physician thought to be a consequence of infantile paralysis. However, there was no history of any other previous infection. In view of the fact that the virus of herpes simplex is a neurotropic virus, the possibility exists that the paralysis might have been a consequence of that infection.

CASE 3 (Table I, Case 73).—J. Z., 8 months of age, was admitted Nov. 15, 1943. Eczema started at the age of 2 months. Three days prior to admission "pimples" began to appear which spread to the neck, arms, hands, and legs. They looked like "chickenpox blisters." The child had been extremely irritable for the past four days. On admission he was found to be suffering from infantile eczema (atopic dermatitis) with the typical umbilicated lesions of Kaposi's varicelliform eruption. The temperature was 104.4° F. Treatment was started with sulfadiazine. The fever subsided but rose again after two days and almost reached 105° F. Sulfathiazole was then instituted and the temperature gradually came down within forty-eight hours. The child improved slowly. There was further elevation of temperature up to 102° F. during the next six days.

The course in the last two cases was very alarming. The children did not respond to sulfonamides in the manner that pyogenic infections usually do. The fever and critical condition continued in spite of adequate dosage. One had the impression that the disease ran its course in spite of the sulfonamides. The first case might indicate a beneficial action of the sulfonamides; they were helpful

TABLE I. MORBIDITY IN INFAN

CASE	HOSPITAL NO.	SEX	AGE			MONTH OF ADMISSION	HOSPITAL DAYS	DIAGNOSIS	TEMPERATURE ON ADMISSION ° F.
			YR.	MO.	WK.				
								Atopic Dermatitis Cases 1	
1	48940	M		2		Jan.	8	Atopic dermatitis	101.2
2	50260	M		11		Jan.	3	Atopic dermatitis	98.8
3	58665	F		5		Jan.	8	Atopic dermatitis	99.2
4	51432	M	2			Jan.	20	Atopic dermatitis	98.4
5	56032	F	1	8		Jan.	8	Atopic dermatitis + intertrigo	98.8
6	51585	M	1	3		Feb.	41	Atopic dermatitis	98.4
7	60963	F		3		Feb.	15	Atopic dermatitis + seborrheic dermatitis	100.2
8	61526	F		4		Feb.	8	Atopic dermatitis + seborrheic dermatitis	100.6
9	60484	M		5		Feb.	7	Atopic dermatitis + seborrheic dermatitis	99.8
10	58869	M		4		Feb.	9	Atopic dermatitis	99.4
11	61672	F		3		Feb.	11	Atopic dermatitis + seborrheic dermatitis	98
12	53852	M		6		Feb.	13	Atopic dermatitis	100.2
13	56388	M	1			March	25	Atopic dermatitis	99.4
14	56387	F	1			March	26	Atopic dermatitis	99.4
15	56399	M	1	4		March	18	Atopic dermatitis	99.4
16	61762	F	2			March	11	Atopic dermatitis	99.6
17	61892	M		9		March	21	Atopic dermatitis	100.
18	59018	M		9		March	25	Atopic dermatitis	99.6
19	59175	F		6		March	27	Atopic dermatitis + seborrheic dermatitis	99.4
20	53919	M	1	4		March	37	Atopic dermatitis	104.4
21	56556	M	1			April	20	Atopic dermatitis	100.2
22	55342	M		6		April	18	Atopic dermatitis	98.6
23	45575	F		9		April	24	Atopic dermatitis	99.
24	51903	F		5		April	16	Atopic dermatitis	99.4
25	59353	M		11		April	17	Atopic dermatitis	100.2
26	59394	M		8		April	27	Atopic dermatitis	98.8
27	56641	M	2			April	18	Atopic dermatitis	99.4
28	59205	F		6		April	25	Atopic dermatitis	103.
29	59215	F	1	6		April	30	Atopic dermatitis	101.2
30	59207	M		4		April	22	Atopic dermatitis	99.2
31	49780	M	1	2		April	24	Atopic dermatitis	98.4
32	51882	M		6		April	17	Atopic dermatitis	99.8
33	56647	M	1	4		April	20	Atopic dermatitis	98.8
34	59018	M		11		May	20	Atopic dermatitis	100.2
35	52176	M		10		May	18	Atopic dermatitis	98.2
36	52099	M		7		May	3	Atopic dermatitis + seborrheic dermatitis	99.6
37	45861	M		9		May	40	Atopic dermatitis	100.2
38	59457	M		7		May	21	Atopic dermatitis	99.6
39	59472	F		7		May	29	Atopic dermatitis	99.6
40	56809	M	1	5		May	7	Atopic dermatitis	99.6
41	62157	M	1	7		May	9	Atopic dermatitis + seborrheic dermatitis	99.6
42	62158	M		11		May	5	Atopic dermatitis	101.8
43	54272	M		4		May	23	Atopic dermatitis	98.8
44	62315	F	1			May	10	Atopic dermatitis	98.8
45	52221	F		5		June	14	Atopic dermatitis	101.2
46	56970	M		7		June	6	Atopic dermatitis	100.6
47	54536	M		5		June	12	Atopic dermatitis	99.6

INFANTILE ECZEMA

TEMPERATURE ON ADMISSION ° F.	HIGHEST TEMPERATURE ° F. AFTER ADMISSION DAY	BLOOD COUNT						COMPLICATIONS		INTERNAL TREATMENT WITH SULFONAMIDES
		HEMOGLOBIN	RED (MILLIONS	WHITE	NEUTROPHILES (%)	LYMPHOCYTES (%)	EOSINOPHILES (%)	ON ADMISSION	AT HOSPITAL	
Dermatitis (Cases 1 to 78)										
101.2	100.2							Intestinal infection		
98.8	99.6	10 9*	4.1	19,250	51	42	6			
99.2	101.8	13.5	4.3	11.200	25	60	8		Gastrointestinal upset	
98.4	102.6	10.9*	4.1	9.300	38	51	8		Cold	
98.8	100.2	12.5	4.9	14.400	61	30	5			
98.4	101.2	8.5*	4.6	20.600	43	21	36			
100.2	101	11.3	3.4	11.300	25	53	16	Streptococcic impetigo	Erysipelas	X
100.6	99.6	12.5	3.7	11.150						
99.8	100.2	13.3	4.9	10.750	16	66	11		Cold	
99.4	99.2	11.3	4.0	15.700				Rickets		
98	101.2	13.1	3.9	13.250	9	22	1		Intestinal infection	
100.2	102.6	11.1	3.8	12.450	38	56	6	Furunculosis		
99.4	101.4	8 8	4.8	16.400	22	57	16			
99.4	100.6	9.0	4.6	10.1	21	70	5			
99.4	100.6	13.9	4.4	8.850	30	58	5		Intestinal upset	
99.6	99.8	11.6	4.4	16.000						
100.	100.4	13.1	5.4	12.500	34	53	10	Impetigo		
99.6	100.2	12.3	4.6	8.200	20	68	7			
99.4	100.	13.1	4.7	16.100	18	60	19			
104.4	104.6	10.4	3.8	11.350	65	28	2	Kaposi's varicelliform eruption + otitis media		X
100.2	101.6	9.9	5.1	10.650	44	42	9			X
98.6	102.4	12.9	4.8	24.300	18	64	8			
99.	101.4	10.9*	5.1	15.000	48	51			Cold	
99.4	99.6	12.7	4.1	12.650	33	52	15	Diarrhea + impetigo		
100.2	103.6	10.9	5.2	16.800				Upper respiratory infection	Acute tonsillitis	X
98.8	99.8	11.1	4.7	19.100	30	44	20	Pyoderma	Bronchitis	X
99.4	99.8	12.5	4.3	7.750	38	48	10			
103.	104.6	11.7	4.8	32.650	76	19		Bronchitis; upper respiratory infection		X
101.2	102.4	9.1	3.9	23.350	47	28	19	Urticaria		X
99.2	102.2	12.1	4.7	26.350	20	68	10		Otitis media	
98.4	100.	9.3*	4.1	12.600	35	48	16			
99.8	100.2	8.8	3.8	15.200	11	19	68			
98.8	100.2	9.3	4.1	19.500	64	31	1			
100.2	100.	16.3	4.1	13.700	24	64	5		Allergic bronchitis	
98.2	103.	9.7	3.4	13.200	35	49	15		Intestinal infection	
99.6	99.4									
100.2	100.	10.9*	4.0	16.750	65	23	10			
99.6	101.4	10.8	4.2	10.950	26	69	5		Bronchitis	
99.6	100.2	10.2	3.1	16.950	25	71	4			
99.6	100.2	10.2	3.8	8.350	32	68				
99.6	100.6	12.1	4.4	13.000	32	64	1			
101.8	101.8	12.7	4.4	12.400	67	30		Cold		
98.8	101.4	13.5	4.2	11.100	24	53	23	Diarrhea		
98.8	99.6	16.3	6.3	21.750						
101.2	99.8	11.9	4.3	12.150	40	41	19			
100.6	103.2	11.3	4.1	8.150	57	38	1	Asthma; upper respiratory infection	Bronchitis	X
99.6	100.2	9.7	4.7	12.150	37	61	1			

TABLE I—CONT'D

CASE	HOSPITAL NO.	SEX	AGE			MONTH OF ADMISSION	HOSPITAL DAYS	DIAGNOSIS	TEMPERATURE ON ADMISSION ° F.
			YR.	MO.	WK.				
48	56964	M		5		June	7	Atopic dermatitis	100.
49	59834	F		7		June	30	Atopic dermatitis	100.6
50	58038	F		2		June	8	Atopic dermatitis	99.6
51	59657	M	1			June	8	Atopic dermatitis	98.6
52	91353	F		4		June	6	Atopic dermatitis + seborrheic dermatitis	98.6
53	56338	M		3		June	2	Atopic dermatitis	99.2
54	52237	F		7		June	7	Atopic dermatitis	101.2
55	44629	M		9		June	42	Atopic dermatitis	100.4
56	46606	F	1			June	8	Atopic dermatitis	100.6
57	59018	M	1	1		July	12	Atopic dermatitis	97.8
58	46172	F		8		July	42	Atopic dermatitis	99.
59	59936	F		10		July	6	Atopic dermatitis + contact dermatitis	98.2
60	54794	M	1			July	47	Atopic dermatitis	98.8
61	54832	M	2			July	30	Atopic dermatitis	100.2
62	53016	F		9		Sept.	9	Atopic dermatitis	100.
63	46636	M	1			Sept.	18	Atopic dermatitis	99.6
64	60893	F		8		Oct.	22	Atopic dermatitis + intertrigo	101.6
65	51871	F		6		Oct.	9	Atopic dermatitis + seborrheic dermatitis	98.4
66	56739	M		5		Oct.	30	Atopic dermatitis + seborrheic dermatitis	99.4
67	52221	F		10		Oct.	26	Atopic dermatitis	100.4
68	51584	M	2			Nov.	5	Atopic dermatitis	98.8
69	51003	M	1			Nov.	5	Atopic dermatitis	100.
70	61074	M	1			Nov.	19	Atopic dermatitis + acute dermatitis	101.2
71	52278	M		5		Nov.	14	Atopic dermatitis + seborrheic dermatitis	99.6
72	60897	F		6		Nov.	20	Atopic dermatitis	99.6
73	61007	M		8		Nov.	33	Atopic dermatitis	104.4
74	51080	F	1			Nov.	11	Atopic dermatitis	99.2
75	55554	F		8		Nov.	33	Atopic dermatitis	98.2
76	53458	F		3		Dec.	17	Atopic dermatitis + seborrheic dermatitis	99.2
77	61173	M		8		Dec.	11	Atopic dermatitis + seborrheic dermatitis	100.2
78	61214	F	1			Dec.	10	Atopic dermatitis + acute dermatitis	100.

*In these cases the hemoglobin originally had been measured in per cent (Tallqvist). For the sake of uniformity it has been changed to grams on this basis: 15:5 grams = 100 per cent.

in regard to the otitis media. Opinions are divided in regard to the value of sulfonamides in this condition.[4, 7] Although it seems doubtful whether the sulfonamides exercise any effect upon the original virus disease, their use seems indicated on account of complicating pyogenic infections.

BLOOD COUNT

The blood count (Table VII) has not shown any significant difference between atopic and nonatopic eczemas, except for the eosinophiles. Mild or marked anemia is not infrequent in severe atopic dermatitis of infants, especially when they have been kept for a prolonged period on a restricted diet. However, in my material, anemia was found just as often in children with skin diseases other than eczema without predisposing them to similar complications.

TABLE I—CONT'D

MPERATURE ON ADMISSION ° F.	HIGHEST TEMPERATURE ° F. AFTER ADMISSION DAY	BLOOD COUNT						COMPLICATIONS		INTERNAL TREATMENT WITH SULFONAMIDES
		HEMOGLOBIN	RED (MILLIONS)	WHITE	NEUTROPHILES (%)	LYMPHOCYTES (%)	EOSINOPHILES (%)	ON ADMISSION	AT HOSPITAL	
100.	100.	13.3	4.5	21.550	24	66	6			
100.6	105.4	11.1	4.4	15.450	32	67	1	Asthma; Kaposi's varicelliform eruption		X
99.6	100.	12.7	5.1	10.550				Bronchitis		
98.6	100.	11.1	5.1	6.200	33	63	11			
98.6	99.2	11.9	3.9	14.250	55	37	6			
99.2	99.6	10.4	3.5	14.800	7	58	29			
101.2	102.6	12.9	3.9	9.450	57	33	8	Impetigo		X
100.4	100.2	11.6*	4.7	11.950	50	48	2			
100.6	105.	10.9*	3.7	10.250	59	40	1	Impetigo		
97.8	101.	12.7	4.3	9.650	33	50	12		Pyoderma	
99.	100.2	11.6*	5.	16.750	47	34	18			
98.2	100.6	12.1	4.1	12.500	37	51	7			
98.8	100.6	9.4	3.	14.600	31	53	16	Asthma		
100.2	100.	13.5	5.2	12.250	39	49	7			
100.	99.	12.7	3.9	9.500	30	65	5			
99.6	100.4	9.3*	4.	13.900	33	55	11			
101.6	102.8	10.8	4.5	14.450	51	34	9	Upper respiratory infection		
98.4	99.8	12.7	4.4	12.600	35	57	8			
99.4	99.4	10.1	4.2	11.650	21	67	8		Gastrointestinal upset	
100.4	104.4	8.5	3.2	8.800				Otitis media		X
98.8	100.4	9.3*	4.9	11.450	51	36	10			
100.	100.	10.9*	4.1	8.300	65	32	3			X
101.2	100.2	13.7	4.6	11.850	58	28	7	Impetigo, pyodermas		X
99.6	100.6	11.1	4.1	9.100	17	77	6		Cold	
99.6	102.8	11.9	4.3	10.600	30	54	15		Cold; intestinal upset	
104.4	104.8	10.0	5.3	8.850	51	41	1	Kaposi's varicelliform eruption		X
99.2	100.	11.6*	3.9	17.550	38	50	10		Intestinal infection	
98.2	103.8	11.9	4.8	13.500	34	48		Streptococcic impetigo	Bronchitis; diarrhea	X
99.2	101.	12.3	3.3	9.100	47	32	18			
100.2	100.2	8.9	4.7	19.850						
100.	100.4	12.7	5.3	14.100	28	70	1			

DISCUSSION AND COMMENTS

1. *Hospital Morbidity of Infantile Eczema.*—My statistics, of 23 per cent complications among hospitalized eczema infants, confirm the high morbidity of this condition as reported by several authors (Table VIII).

Even if our figures, like those of Glaser and Edwards,[2] are far below those of the other two authors, they are still very impressive. We can only speculate why the variations of the morbidity rate are so great. The conditions under which infants with eczema are managed are more favorable to cross-infection at some places than at others. Minor complications may have escaped the attention in some instances. However, the temperature data in my statistics indicate that apparently no serious complications have been overlooked.

To the question, "Why do children with eczema develop complications?" this paper gives a definite answer.

TABLE I

CASE	HOSPITAL NO.	SEX	AGE			MONTH OF ADMISSION	HOSPITAL DAYS	DIAGNOSIS
			YR.	MO.	WK.			
								Other Eczemas—Cases 79 to 100
79	58646	F		11		Jan.	5	Seborrheic dermatitis
80	53747	F	1	1		Feb.	7	Contact dermatitis (epidermitis)
81	51565	F			6	Feb.	19	Intertrigo
82	45499	F		3		March	8	Seborrheic dermatitis
83	61870	M		4		March	17	Seborrheic dermatitis
84	49908	F			7	April	68	Seborrheic dermatitis + intertrigo
85	56648	F		10		April	3	Dermatitis
86	51928	M		8		April	14	Seborrheic dermatitis
87	53889	M			5	April	24	Intertrigo
88	62103	F	2			April	5	Contact dermatitis (epidermitis)
89	56846	M		2		May	12	Contact dermatitis? (epidermitis)
90	49993	M		10		May	7	Seborrheic dermatitis?
91	54341	M		2		May	12	Contact dermatitis (epidermitis)
92	59679	F			2	June	2	Contact dermatitis? (epidermitis)
93	59950	M			6	July	3	Contact dermatitis (epidermitis)
94	53166	F	2			Oct.	4	Dermatitis
95	59286	M	1	4		Oct.	31	Seborrheic dermatitis?
96	49908	F		7		Oct.	9	Seborrheic dermatitis
97	61096	M		6		Nov.	23	Seborrheic dermatitis
98	61099	F			5	Nov.	5	Seborrheic dermatitis
99	59486	M		6		Nov.	25	Intertrigo
100	55685	M			5	Nov.	24	Intertrigo

*See footnote, Table I.

We have noted two kinds of complications (Tables V and VI): skin infection on one side, and respiratory and gastrointestinal disturbances on the other. In regard to the first group, skin infections such as impetigo, pyodermas, and others, there can be no doubt that the diseased skin is responsible. The type of eczema is apparently of no importance. These secondary skin infections are common in eczematous children before hospitalization. Among hospitalized infants, the incidence of additional skin infections is negligible.

But when it comes to respiratory and gastrointestinal disturbances, the story is entirely different. These are the complications that plague the wards, because they are acquired largely at the hospital. They occur nearly exclusively among the atopic children. There were twenty-two such complications among seventy-eight children with atopic dermatitis and only one among twenty-two children with nonatopic eczemas. It is, therefore, evident that it is not the diseased skin that predisposes the children to these infections. What, then, makes the atopic child so susceptible to these complications? The answer is the atopic constitution. It is the capacity of the atopic individual to develop other atopic sensitivities, especially of the respiratory and gastrointestinal tracts.

It is well known that infants with atopic dermatitis suffer frequently from major or minor respiratory allergies. Gastrointestinal allergies also play an important role in atopic infants, apparently more than is generally realized. A careful history of the babies with infantile eczema often reveals a story of previous intestinal upsets, apparently due to some food intolerance. Minor degrees of food allergy may be manifested only by flatulence or more frequent and foul-smelling stools. The allergic nature of these symptoms is well known

TABLE I

TEMPERATURE ON ADMISSION ° F.	HIGHEST TEMPERATURE ° F.	BLOOD COUNT						COMPLICATIONS		INTERNAL TREATMENT WITH SULFONAMIDES
		HEMOGLOBIN	RED (MILLIONS)	WHITE	NEUTROPHILES (%)	LYMPHOCYTES (%)	EOSINOPHILES (%)	ON ADMISSION	AT HOSPITAL	
97.8	99.6	10.4	4.8	10.800	19	67	7	Scabies		
97.2	100.4	11.9	5.1	9.100	64	32	4			
100.2	100.4	9.3*	4.	8.200	34	58	5			
99.8	100.4	10.1*	5.1	17.850						
104.6	100.	12.3	4.5	12.600						X
100.	100.	10.9	4.2	12.600	63	49	4			X
99.	100.8	12.3	4.9	6.900	36	54	6	Staphylococcic impetigo		
101.6	102.2	10.8	4.4	14.370				Streptococcic impetigo		
101.2	100.4	9.7	2.4	5.650	57	40				
99.	99.6	14.8	4.6	9.950	15	68	8	Erysipelas		X
99.	100.	10.2	3.8	13.000	29	52	12	Pyoderma		
99.2	99.4	7.8*	3.	16.050				Acrodynia?		
98.	99.8	12.7	3.2	10.250	45	67	4			
99.6	99.6	21.7	5.8	9.700	35	47	10			
99.2	99.4							Staphylococcic impetigo		
98.4	99.7	13.5	4.	14.700				Impetiginized		X
99.	102.8	8.2	3.5	12.950				Scabies	Upper respiratory infection	X
98.2	99.2	10.9*	4.	11.900	35	65				
101.	101.2	11.3	4.2	10.450	60	26	5	Coryza		X
98.6	100.2	12.9	4.5	11.150	24	68	3			
99.8	100.	8.5	4.7	12.400	52	45		Pyoderma		
99.2	100.	12.3	4.6	13.750				Impetigo		

as far as adults are concerned. The role they play in atopic children was brought to my attention rather accidentally. I noticed that our head nurse fondly nicknamed many of my infants with eczema "Stinky." These babies had frequent stools of a peculiar odor. In most instances we were able to demonstrate a food allergy and to straighten out the affair by dietary restrictions.

It thus becomes rather simple to explain the hospital complications of the atopic child. These children suffer at the same time from respiratory and gastrointestinal allergies, which remain subclinical in some instances; like other patients with these allergies they are more prone than normal people to acquire bacterial infections of the respiratory and gastrointestinal system. What clinically impresses us as a new disorder actually is an exacerbation or complication of the underlying process. These children develop at the hospital the same respiratory and gastrointestinal complications as at home (Tables V and VI). This explanation seems rather satisfactory to me.

Recognition of these respiratory and gastrointestinal infections as atopic complications indicates that even the best precautions instituted at the hospital may not completely eliminate the morbidity of infantile eczema of the atopic type. In these children the external infection apparently plays only a minor part. Even so, we may expect that methods to cut down the danger of cross-infections in a hospital will also decrease the rate of complications in atopic children.

2. *Hospital Mortality of Infantile Eczema.*—There are only a few statistics about hospital mortality of infantile eczema. Koch and Schwartz[1] reported a mortality rate of 14.5 per cent, Glaser and Edwards,[2] 4.7 per cent, Schwartz-

TABLE III. MORBIDITY OF SE[illegible] DISEASES

CASE	HOSPITAL NO.	SEX	AGE			MONTH OF ADMISSION	HOSPITAL DAYS	DIAGNOSIS
			YR.	MO.	WK.			
								Erysipelas
1	45480	M	1			March	4	Erysipelas
2	45670	M		8		April	41	Erysipelas
3	43461	F	1			May	6	Erysipelas
4	62280	F	1	5		May	5	Erysipelas
5	46128	F		8		July	7	Erysipelas
6	48203	M	1	3		October	7	Erysipelas
								Impetigo + Pyodermas
7	52565	F	2			March	4	Impetigo + pyoderma
8	49896	M		2		April	5	Impetigo – staphylococcic
9	51986	F	2			April	10	Impetigo – streptococcic pyoderma
10	61847	F			2	April	10	Impetigo – staphylococcic
11	91477	M	1	5		June	2	Impetigo – staphylococcic
12	45499	F	1	7		July	4	Impetigo – staphylococcic
13	55417	M		11		Oct.	6	Impetigo – streptococcic
14	54733	M	1			Nov.	13	Impetigo
15	45296	M		6		Feb.	8	Impetiginized herpes
16	46080	M	1			July	6	Herpes, secondary infection
								Varia
17	59534	F		3		May	11	Infected hemangiomas
18	59534	F		3		May	10	Infected hemangiomas
19	53315	M	1	6		June	3	Urticaria
20	62264	M	1			May	5	Vaccinia generalized
21	54013	M			1	March	9	Toxicoderma

*See footnote, Table I.

man and associates,[3] 3.3 per cent. In our one hundred cases treated at St. Joseph's Hospital there was no death.

It is somewhat disappointing for the dermatologist that he cannot claim any credit for this result. In my opinion the fortunate outcome is due mainly to two factors: in the first place, and chiefly, to the sulfonamides; and in the second place, and to some extent, also to the excellent care of our nursing staff.

The beneficial effect of the sulfonamides in respiratory infections is too obvious as to require discussion. Twenty-two infants in our series received sulfonamide therapy. The excellent nursing care afforded to the infants with infantile eczema must be stressed. We have been fortunate to have throughout these years the same very competent supervisor of the pediatric ward. This Sister has not only become an expert in handling infants with infantile eczema, but also they have become her pets and are as closely watched as can be. Although the dermatologist is in charge of all children with infantile eczema, they are all examined by the pediatrician. The latter is called in again routinely when the slightest complication arises. Furthermore, whenever feasible, the eczematous children are separated from the other pediatric patients. Care is taken that these children are not exposed to draft and not chilled during treatment. An electric heater is placed near them. The infants are usually treated by the same nurses who are especially assigned for this work.

The significant point of my statistics seems to me that since the advent of the sulfonamides, death from eczema has become an avoidable complication. In order to demonstrate that point I shall analyze briefly the instances of death

DISEASES OTHER THAN ECZEMA

MPERATURE ON DMISSION ° F.	HIGHEST TEMPERATURE ° F.	BLOOD COUNT						COMPLICATIONS		INTERNAL TREATMENT WITH SULFONAMIDES
		HEMOGLOBIN	RED (MILLIONS)	WHITE	NEUTROPHILES (%)	LYMPHOCYTES (%)	EOSINOPHILES (%)	ON ADMISSION	AT HOSPITAL	
104.4	104.4									X
103.4	105.4	9.3*	4.	8.600	29	71		Abscesses		X
106.	105.6									X
105.6	101.	10.6	4.7	17.850	74	16	2			X
103.6	103.	10.9*	4.0	10.000	40	60				X
102.	100.4	10.9*	4.5	9.100						X
99.6	99.4	13.1	4.3	10.300	63	33				
99.4	99.8	9.3*	2.4	8.050	59	41				
100.	100.4	11.5	4.2	17.050	73	24	3			
98.6	99.8	16.0	5.0	35.200	72	21	2			
99.2	99.8	10.4	5.2	6.250	61	36	3			
104	103.	11.6*	4.0	5.750	45	50				
101.2	99.8	11.7	3.6	5.000						
98.4	100.4	12.1	4.0	8.250						X
99.	99.									
101.8	100.8	11.6*	4.5	7.000						
104.6	105.	10.0	3.4	30.950	73	20	1	Streptococcic sore throat		X
102.2	103.6	9.4	3.7	26.350	65	32	1	Nephritis		X
102.4	100.4	8.9	4.4	5.550	39	58	1			
104.4	103.8	9.1		11.800	36	61				
98.	99.4									

from eczema as reported in the literature. For this purpose we may divide them into three groups: (1) death in children with eczema admitted to the hospital with severe complications, (2) death in children with eczema admitted without complications, (3) the so-called "sudden death" from eczema ("Ekzemtod" of the German literature).

1. *Death From Pre-existing Complications.*—It does not seem proper to place the responsibility for the fatal outcome in these cases on the eczema or the hospital. For instance, two patients (Cases 34 and 60 of Glaser and Edwards[2]) with eczema and suffering from erysipelas and pneumonia, respectively, died shortly after admission to the hospital. It is safe to assume that they would also have done so if they had been left at home. In fact, all of Glaser and Edwards' deaths from eczema occurred among children admitted with complications. Their actual hospital mortality rate for children hospitalized only on account of eczema is zero.

This report is the only one covering the sulfonamide era. It indicates that the mortality even among children admitted with complications can be practically eliminated, because the most dangerous of these, severe respiratory infection and erysipelas, are well controlled by the sulfonamides. The change brought about by these drugs is well demonstrated in our erysipelas series (Table III). The former high infantile mortality from this infection is well known. All six children with erysipelas recovered—undoubtedly due to sulfanilamide.

2. *Death in Eczematous Children Arising from Infectious Complications Acquired at the Hospital.*—Analyzing these cases we find that practically all

TABLE IV. INCIDENCE OF COMPLICATIONS IN VARIOUS GROUPS OF INFANTS HOSPITALIZED FOR DERMATOLOGICAL CONDITIONS

DIAGNOSIS	NUMBER OF CASES	COMPLICATIONS	
		TOTAL	PER CENT
Atopic dermatitis (see Table I)	78	22	28.3
Other eczemas (see Table II)	22	1	4.5
Skin diseases other than eczema (see Table III)	21	0	0

TABLE V. NATURE OF HOSPITAL-ACQUIRED COMPLICATIONS OF CHILDREN WITH INFANTILE ECZEMA

FORM OF ECZEMA	SKIN INFECTIONS	RESPIRATORY INFECTIONS*	GASTRO-INTESTINAL DISTURBANCES
Atopic dermatitis (Cases 1 to 78)	2	12	8
Other eczemas (Cases 79 to 100)	–	1	–

*Cold, tonsilitis, otitis media, bronchitis.

TABLE VI. CLASSIFICATION OF COMPLICATIONS PRESENTED BY THE ECZEMATOUS INFANTS UPON ADMISSION TO THE HOSPITAL (THIRTY-NINE COMPLICATIONS IN THIRTY-SIX INFANTS)

FORM OF ECZEMA	SKIN INFECTIONS*	RESPIRATORY INFECTIONS†	GASTRO-INTESTINAL DISTURBANCES	OTHER COMPLICATIONS‡
Atopic dermatitis (Cases 1 to 78, Table I)	12	10	3	2
Other eczemas (Cases 79 to 100, Table II)	10	1	–	1

*Impetigo, pyodermas, furuncles, erysipelas, scabies, Kaposi's varicelliform eruption.
†Cold, upper respiratory infections, otitis media, bronchitis, asthma.
‡Rickets, acrodynia, urticaria.

TABLE VII. RESULTS OF BLOOD COUNTS IN ATOPIC AND NONATOPIC ECZEMAS

TEST	ATOPIC ECZEMAS (TABLE I) (%)	NONATOPIC ECZEMAS (TABLE II) (%)	CONTROLS: OTHER SKIN DISEASES (TABLE III) (%)
Slight anemia*	27.6	9.5	29.4
Marked anemia*	32.9	28.6	47.1
Total anemia	60.5	38.1	76.5
Leucocytosis (over 12,000)	56.6	47.6	29.4
Lymphocytosis (over 45%)	65.2	71.4	38.5
Average eosinophilia	9.7	4.9	0.9

*The following values were considered normal: Red count 4,200,000; hemoglobin 11.0 Gm. for children less than 4 months and 12.0 Gm. for children over 4 months. Hemoglobin readings more than 1.0 Gm. below the normal values were considered as signs of marked anemia, especially when the red count was also below normal. The figures for normal values are somewhat arbitrary; they were based on the average values as given by Kracke,[8] and by Mackay.[9]

TABLE VIII. MORBIDITY OF INFANTILE ECZEMA IN VARIOUS LOCATIONS

	ECZEMA—ATOPIC DERMATITIS				CONTROLS (BOARDERS) (NON-ECZEMAS)	
Location	Milwaukee, Wis.	Rochester, N. Y.	New York, N. Y.	Marshfield, Wis.	New York, N. Y.	Marshfield, Wis.
Author	Koch and Schwartz[1]	Glaser and Edwards[2]	Schwartzman and associates[3]		Schwartzman and associates[3]	
Total number of cases	103	106	33	100	111	21
Percentage of hospital-acquired complications	43.6	20	60.6	23	6.4	0

children died from complications that could have been prevented or that would have responded to sulfonamides if they had been available at that time. The statistics of Glaser and Edwards, as well as mine, indicate that this cause of death can be actually eliminated with proper care and especially with the help of the sulfonamides.

3. *Sudden Death from Eczema.*—There remains a group of deaths from eczema that do not fall into the two categories we have mentioned. A certain degree of mystery cloaks these cases. They are usually referred to as "sudden death from eczema," corresponding to the "Ekzemtod" of the German literature. These deaths are reported to occur very suddenly and no cause for them can be found. They have been known for over a century and also have been reported recently (Davies[10]). They have occurred in and out of the hospitals. Many experienced dermatologists (Jadassohn[11]) have never seen them. I, too, cannot recollect ever having come across one. However, the authenticity of the reports cannot be doubted. Many theories have been advanced, most investigators presenting rather one-sided ideas based on the one or rather few cases of their own experience. To be sure, all cases so reported are not alike. Quite a few can be definitely explained, by the clinical course or the pathologic findings, as due to infectious complications. But there remains a definite entity of sudden death from eczema without explanation. The term sudden "death" is somewhat misleading, as some children experience similar crises from which they recover. Davies[10] described these incidents as follows: The accident is peculiar to infants with infantile eczema. It occurs during the first year of life. Most of the cases occur in the spring. Nearly all, if not all, take place in hospitals or away from the mother. The accidents usually occur within the first few days of hospitalization. Autopsy does not disclose sufficient cause of death. These incidents apparently occur when the babies are in the care of some physicians and not of others. According to Davies usually the first definite change noticed is restlessness and pallor with or without cyanosis. Dyspnea soon becomes obvious and may be intense. Vomiting also is frequent and convulsions may occur. The temperature rises rapidly to 103° F. or more. The infant becomes collapsed and unconscious; the lips are blue; the skin, rigid; and the extremities, cold. Death occurs rapidly. However, according to Davies[10] not all these accidents terminate fatally. Some patients have recovered. The child may even become comatose and yet the following day present a normal aspect and take his food as usual. Many theories have been proposed. Bernheim-Karrer,[12] basing his opinion on findings of one case of his observation, would like to explain the death as due to an infectious myocarditis. However, in his case there was secondary pyogenic infection of the eczema present. Feer[13] considered status thymolymphaticus responsible for the eczema death. Davies[10] was inclined to think of a psychic trauma. Schwartz[14] analyzing ten eczema deaths, believed that fulminating septicemia might have been the cause; however, many of his cases apparently do not belong to the group here under discussion. Hutinel[15] considered anaphylactic shock. Moro[16] thought of disturbances in the parasympathetic nervous system ("Vagustod"). Moro pointed out that most of the deaths in Feer's and his statistics had occurred in the early months of the year. However, Moro considered the vagotonic factor only part of the picture. He believed that local treatment was also responsible. Moro warned, therefore, against extensive external treatment of eczema in the spring.

From early times, treatment of the eczema has been considered a causal factor, because the death occurred after local treatment was instituted. The children with eczema were considered *noli me tangere* by Steiner[17] in the early nineteenth century. But even in modern times external treatment is considered a factor in these accidents. Interference with cutaneous respiration by ointments covering the whole body had been suggested by Bloch, Simon, and Castendoz[18] and by Cameron.[19] Sulzberger[20] suggested the possibility of poisoning from phenollike tar products. According to Meyer and Gottlieb,[21] phenol poisoning leads to paralysis of the central nervous system. It begins with vertigo, headache, vomiting. In severe cases cyanosis follows after a few hours, with cold sweats, small, frequent pulse, collapse. The outcome is either death or rapid complete recovery. A comparison of this description with that of sudden death from eczema as given by Davies,[10] reveals a great resemblance of the two conditions. Sulzberger[20] stressed the fact that treatment of these children is frequently carried out in general wards with supervisors not familiar with the special problem. Tar is a rather toxic product and should not be used on too large a surface. Still some hospitalized children are treated with tar or tar ointment all over the body. One must remember that phenol is very rapidly absorbed from the skin. Phenol is much more toxic when it enters the body through the skin than when taken orally because it enters the circulation without passing through the liver. The liver detoxifies the phenol by forming conjugated sulfuric and glycuronic acids. Such a toxic theory—especially in combination with interference with cutaneous respiration and lability of the autonomous nervous system—would explain satisfactorily the symptoms as well as the other circumstances of some of the acute deaths from eczema. It would also explain why these cases of eczema deaths occur only in some hospitals or with some doctors and not with others. The lack of post-mortem findings also fits in well with this theory. There are no pathologic changes characteristic of acute phenol poisoning. I have stressed this point, in spite of its hypothetical nature, because we are not fully aware of the toxicity and dangers from treatment with coal tar. It is important, especially in children, not to use tar over too great a surface, especially if this surface is eroded. It is a good rule to use tar on not more than two extremities at a time.

SUMMARY AND CONCLUSIONS

1. Among one hundred consecutive hospital admissions of infants with eczema, from 1937 to 1944, no deaths occurred.

2. Out of these one hundred children, twenty-one suffered from twenty-three complications, a morbidity of 23 per cent.

3. A breakdown of the statistics showed that all but one of the complications occurred among the seventy-eight atopic children and only one among the twenty-two nonatopic eczemas.

4. Nearly all complications were respiratory infections or gastrointestinal disturbances. They are explained as exacerbations of concomitant respiratory or gastrointestinal allergy.

5. The statistics presented demonstrate that with the advent of sulfonamides and under proper nursing care, there need not be fear of death in hospitalized infants with eczema. This conclusion should not lead to indiscriminate hospitalization of cases of infantile eczema, but it should eliminate fear in those instances where hospitalization becomes mandatory on account of the severity of the eczema, or for other reasons.

6. The so-called "sudden death from eczema" is discussed. A hypothesis of toxic effects from phenollike tar products, in combination with interference with skin respiration and disturbance of the autonomous nervous system, is suggested to explain some instances of this phenomenon. A reminder is given about the toxicity of coal tar and it is suggested that tar preparations should not be used over too great surfaces.

I am indebted to Dr. Jerome Glaser for his suggestion to publish this series and for his friendly advice.

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SERUM IN THE PROPHYLAXIS OF CONTACTS AND THE TREATMENT OF WHOOPING COUGH

JOSEPH H. LAPIN, M.D.
BRONX, N. Y.

THE efficacy of *Hemophilus pertussis* vaccines in the routine prophylaxis of whooping cough has been demonstrated in every large series. Its acceptance by the medical profession is attested by the recent favorable report of the Council of Pharmacy and Chemistry.[1] In spite of this, there still seems no unanimity on the need for specific serum in the passive immunization of contacts to whooping cough nor in the treatment of the disease. For example, diphtheria toxoid[2] and adrenal cortex[3] have been recently advocated for the treatment of whooping cough. The use of such nonspecific agents testifies to the fact that the medical profession is as yet unacquainted with specific serum therapy in pertussis.

Such vaccine fractions as Topagen, U.B.A., and Pertussis Antigen (Lederle) have had their day in both prophylaxis and treatment. However,

since Dow's convincing animal experiments[4] showing a marked loss of immune principle in these factors, and since carefully controlled clinical reviews[5] showing their inefficacy in both prophylaxis and treatment, no recent workers have been using these products.

At present, we have both human and rabbit serums, either antibacterial alone or both antibacterial and antitoxic, available for the passive immunization of contacts and the treatment of active cases. A recent review of theoretical considerations involved is given by McGuinness, Armstrong, and Felton.[6] The only recent report of work with a *rabbit antitoxin* pure and simple (that is, containing no antibacterial antibody because prepared by immunizing rabbits with a special "antitoxin") has been that of Bullowa and Alterman.[7] These authors found rabbit "antitoxin" capable of preventing whooping cough when given early in the incubation period and prior to the onset of cough but of little value in reducing paroxysm. No details of exposures are given and the method of preparation seems theoretically unsound.

An *antibacterial pertussis rabbit serum* prepared by immunizing rabbits with *H. pertussis* organisms was reported by Bradford, Scherp, and Brooks[8] to have protected 65 per cent of twenty sibling familial infant contacts. This figure is slightly less than that achieved with human serum by McGuinness and associates[6] and the procedure presents the added dangers of animal serum sensitization. The only report on treatment with this serum found in the literature was a recent one by Bradford, Brooks, and Katsampes.[9] Four groups of eleven infants each were studied; the first group received sulfadiazine; the second, antibacterial rabbit serum; the third, both sulfadiazine and serum; and the fourth served as controls. While sulfadiazine and the antibacterial serum each caused definite clearance of the organism from the nasopharynx, the combined form of therapy resulted in a prompt and lasting effect. While these results are unquestionably good, the use of rabbit serum is still objectionable on the grounds of sensitization.

An *antitoxic and antibacterial pertussis rabbit serum*, prepared by injecting rabbits with pertussis toxin prepared by the Strean method[10-12] and with *H. pertussis* vaccine, has been used for the prophylaxis of contacts and the treatment of active whooping cough. These reports[10-12] show fair results in a small number of contacts given 10 c.c. of the serum and good results in a small number of active cases of the disease. The question of the true nature of the pertussis toxin Strean has used depends on long experience with the skin tests he recommends, and many more cases will be needed to test the validity of his assumption that the true toxin of pertussis is being employed. My personal experience, because of fear of animal serum sensitization, has been limited to only six cases. Results, using a 10 c.c. dose at two-day intervals for two doses, have been good in four cases and questionable in two.

The use of *hyperimmune antibacterial human serum*, whether unconcentrated or lyophile, was reviewed by me[5] last year. Scheinblum and Bullowa[13] recently reported twenty-three ill children, receiving from one to four 20 c.c. doses of the lyophile human serum, with 52 per cent good and 26 per cent moderate responses. McGuinness and associates,[6] using two injections of 20 c.c. from three to five days apart, protected 67.9 per cent of 137 familial contacts. The same authors using from three to four injections of 20 c.c. at two-day intervals in active cases, reported 38.5 per cent excellent and 31.7 per cent good results. The serum was given intravenously in much larger doses in critically ill children. The experiences of these authors as well as my own confirm the

general impression that a large majority of contacts can be protected and a large percentage of children sick with whooping cough can be substantially relieved by hyperimmune human whooping cough serum, which is procurable in the lyophile state from the Philadelphia Serum Laboratory. The disadvantages are: first, that a constant supply of the serum will be difficult to secure if used on a large scale, and second, that the administration of a 10 c.c. volume (lyophilized residue of 20 c.c. of human serum resuspended in 10 c.c. of diluent) is painful. Repetition of this 10 c.c. dose at frequent intervals becomes a struggle. For this reason, even though no animal serum or other reactions were observed and clinical results were satisfactory, many physicians have been loath to employ this method.

The use of *hyperimmune antibacterial human serum* as the *globulin fraction* was a natural aftermath of Cohn's[14] electrophoretic demonstration that the antipertussis antibodies are part of the gamma globulin. By a salt fractionation method applied to the concentration of pooled sera, approximately ten times the concentration of agglutinating antibodies is achieved.[15] An application of the Cohn fractionation method permits approximately twenty times the concentration and will be used on this product in the very near future. Even with a tenfold concentration the immune bodies of 25 c.c. of human hyperimmune pertussis serum can be delivered in 2.5 c.c. of the globulin fraction, in an ordinary hypodermic injection. I am reporting on the use of this product* in the prophylaxis of ten contacts to whooping cough and in the treatment of twenty-five active cases of whooping cough.

The ten contacts to whooping cough were all intimate, familial, sibling cases, between the ages of 4 months and 13 years, who had never had the disease. In each case the first injection was given before the infecting sibling had reached the paroxysmal stage, usually after about seven days of a suspicious cough. In these ten contacts, the diagnosis of whooping cough in the sick sibling was afterwards confirmed by the clinical course of the disease. Prophylaxis or passive immunization consisted in two doses of 2.5 c.c. of the globulin fraction given at two-day intervals. There were no reactions, either local or general. Of the ten contacts, seven were completely protected and three developed a mild type of paroxysmal cough. None vomited, whooped, or had cyanosis. One of these three did not receive the first injection until thirteen days after the first exposure.

The twenty-five active patients with whooping cough ranged from 4 months to 31 years of age, with two (8 per cent) under 6 months, twelve (48 per cent) from 1 to 5 years, eight (32 per cent) from 6 to 10 years, and three (12 per cent) from 11 to 31 years. Results (Table I) were graded as marked improvement, moderate improvement, or no improvement, depending on the complete cessation of whoop and vomiting after treatment; eleven (44 per cent) showed marked improvement on this scale; seven (28 per cent) showed moderate improvement; and seven (28 per cent) no improvement under the treatment given. From one to five injections of 2.5 c.c. of the globulin fraction were given at forty-eight-hour intervals, with no reactions of any kind noted.

*"Hypertussis" (Cutter Laboratories, Berkeley, Calif.,) is the globulin fraction of hyperimmune pertussis human serum. Healthy donors who have had whooping cough in childhood are given a series of twelve weekly injections of forty billion *H. pertussis* vaccine. They are bled three weeks after the last dose, rested for six weeks, given a booster dose of forty billion, bled the following week, rested for eight weeks, given a booster dose and bled the following week. The pooled sera have an agglutination titer of 1:1,280 or better (J. J. Miller, Jr., method). So far the globulin has been recovered from the serum by a modified ammonium sulphate fractionation method. The approximate concentration method as measured by agglutination titers shows a tenfold increase.

TABLE I

PATIENT	AGE (YR.)	DURATION COUGH BEFORE TREATMENT (DAYS)	INJECTIONS GLOBULIN FRACTION (2.5 C.C.) AT 2-DAY INTERVALS	CLINICAL RESULTS				IMPROVEMENT GRADED AS		
				WHOOP	VOMIT	CYANOSIS	DURATION COUGH (WK.)	MARKED	MODERATE	NONE
D. W. (H. K.)	31	14	1	0	0	0	4	v	–	–
P. W. (H.K.)	10	24	1	0	0	0	4	v	–	–
D.M. (H. K.)	4	6	2	v	v	0	4	–	–	v
R. P.	3	14	2	v	v	0	4	–	v	–
D. R.	4	2	3	0	0	0	4	v	–	–
P. T.	4	17	3	0	0	0	4	v	–	–
L. T.	3	14	3	v	v	0	5	–	v	–
D. M.	3	17	5	0	v	0	5	–	–	v
R. Z.	4	10	2	0	0	0	2	v	–	–
A. T.	9	25	2	v	v	0	5	–	–	v
H. B.	4	12	2	0	v	0	5	–	v	–
R. G.	0.3	7	4	0	0	0	4	v	–	–
B. L.	0.4	13	4	v	v	0	5	–	–	v
S. R.	2	11	3	v	0	0	5	–	v	–
H. S.	1	14	3	0	0	0	2	v	–	–
R. P.	2	20	2	0	v	0	5	–	v	–
J. S.	2	16	2	v	v	0	5	–	–	v
J. F.	16	14	2	0	0	0	3	v	–	–
R. G.	16	10	2	0	v	0	4	–	–	v
B. E.	8	12	2	v	v	0	5	–	v	–
B. I.	6	14	2	0	0	0	4	v	–	–
S. S.	7	12	2	v	v	0	4	–	v	–
B. L.	8	8	2	v	v	0	4	–	–	v
F. O.	7	11	2	0	0	0	4	v	–	–
S. T.	6	17	2	0	0	0	4	v	–	–

"v" indicates yes.

Tests have been made on the production of a human hyperimmune serum prepared by the injection of agglutinogen alone, and this will be compared with hyperimmune serum obtained by the injection of vaccine alone.[16] This development will require further testing.

CONCLUSION

A wide choice of specific serum therapy is now available for the prophylaxis of contacts and for the treatment of active cases of whooping cough. The results with antitoxin, antibacterial pertussis rabbit serum, antitoxic and antibacterial pertussis rabbit serum, and hyperimmune antibacterial pertussis human serum have been reviewed. The results in prophylaxis and treatment of a new globulin fraction of hyperimmune antibacterial pertussis human serum are recorded. In the prophylaxis of contacts, 70 per cent of ten intimate, familial, sibling susceptibles were protected and 30 per cent had mild cases. In the treatment of active cases of whooping cough, in 44 per cent of twenty-five cases there was marked success; in 28 per cent, moderate improvement; and in 28 per cent, no improvement. The use of larger doses of the serum together with sulfadiazine should result in striking success in the prophylaxis of contacts and the treatment of active cases of whooping cough.

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ADDENDUM

Since submission of this report, twenty more patients with whooping cough have been treated by injections of Hypertussis and sulfadiazine with definitely better results than reported here. Five of these were infants under 6 months of age.

PSYCHIATRIC EVALUATION OF THE HYPERKINETIC CHILD

WILMOT F. SCHNEIDER, M.D.
CLEVELAND, OHIO

IT MATTERS not whether we are teacher, parent, school or private physician—we are all familiar with the hyperkinetic child. Many of you may not recognize him by that name. Some of you may know him as the "nervous" child, or as the one who "never sits still"; others call him hypomanic or the "fidgety child."

The term hyperkinetic child is applied in this study to those restless, overactive, aggressive, distractible children whose behavior includes inattention, flightiness of ideas, an explosiveness of motor output; those whose behavior in the school, home, and doctors' examining rooms includes unpredictable, impulsive behavior, hair-raising "getting into everything." Hyperkinesia carries a connotation of more than the "superfluous or inappropriate movements" described by Hobhouse[1] as characteristic of "fidgetiness." These localized movements are the ties and habits, the "non-choreic hyperkinesia of fidgety children," representing possibly, as Krasnogorski pointed out, "the balance between cerebral excitability and infracortical inhibition has been disturbed by some environmental factor, resulting in a temporary ineffectiveness of the latter." Hyperkinetic behavior is more akin to the impulsive, postencephalitic type of behavior disorder described by Ford[2] but not carried to the destructive ends nor showing the uncontrolled motor drive or entire lack of judgment so frequently seen in the postencephalitic (Von Economo epidemic encephalitis) or posttraumatic behavior disorder.

Dr. Lurie[3] addressed a similar meeting, the Fourth Institute on the Exceptional Child, in 1937. He spoke about "Endocrinology and the Understanding and Treatment of the Exceptional Child." Without hesitation he pointed out, "The trend at present in child guidance work is apparently toward the psychological or, more specifically, toward the psychoanalytic interpretation of

From the Babies and Children's Hospital, and the Departments of Pediatrics of the University Hospitals and Western Reserve University School of Medicine.
Read in part before the Eleventh Institute on the Exceptional Child of the Woods Schools, Langhorne, Pa., in Cleveland, Ohio, Oct. 25, 1944.

behavior disorders in children." However, from his own experience, he stressed that 49 per cent of the behavior cases (1,000 cases reviewed) studied in the Cincinnati Child Guidance Clinic had endogenous (psychophysical) causative factors; approximately 75 per cent of these were found to have an organic etiology. We, then, as parents, teachers, school administrators, school physicians, pediatricians, and psychiatrists are faced with this *physical* aspect of the maladjusting child. We cannot deny the absolute necessity of studying the total psychobiologic[4] personality make-up of the deviant child. We must know him or her as a psychobiologic unit; an integration of the psyche (emotions and intelligence) and soma (physicochemical components, endocrine, allergy) being acted upon by the total environment (home, school, society) and in turn having an effect, as a personality, on this environment.

We cannot deny that the emotions and emotional development are inseparably integrated in the behavior of the antisocial, aggressive or withdrawn, nonconforming culprit who disrupts the office routine, home, or classroom. Our challenge is to understand these emotions: what they mean and what may be contributing to make these emotional reactions unhealthy and unacceptable. No pediatrician should avoid the responsibility of understanding the emotional content of behavior,[5] nor should he overlook the finer integration of minor forms of ill health as these contribute to this emotional imbalance. The child guidance worker well recognizes that relatively minor physical defects in the average, well-balanced child can be singly, or even in number, assimilated and integrated into the healthy emotional behavior. In contrast we see the emotionally labile children who may live in a poor school or home environment suddenly precipitated into total maladjustment when one or two minor physical defects, or many little factors, combine to be the "straw that broke the camel's back."

Attempting to more fully evaluate the role of physical factors as primary in causing behavior disorders or highly important in contributing to psychobiologic malfunction, I have reviewed textbooks, systems, and the general literature of child psychiatric disorders. The pediatrician, educator, and orthopsychiatrist will agree that such articles are thinly dispersed.[6]

Confronted with the hyperkinetic child twenty years ago, the teacher was sure the child had either St. Vitus Dance or pinworms, or, if a boy, needed circumcision. Today our hyperkinetic, easily distractible and distracting, overactive, classroom disturber is still with us. He is a disrupting influence in the even more crowded classrooms (the 1944 teacher shortage). He is unwelcome in the too-busy pediatrician's office. He offers a challenge to the entire diagnostic procedures of the mental hygiene clinic. He is the child for whom special classes have been formed in New York City[7] and for whom the private boarding school[8] becomes a haven for continued study, treatment, and reeducation toward a return to society as an adjusted, integrated member rather than a misfit and potential delinquent.

The investigation of these hyperkinetic children has necessarily been with the psychobiologic approach clearly in mind. A precise history serves to orient the examiner in the hereditary structure of the child's personality, and to acquaint him with the earliest traumata (prenatal, birth, immediately postnatal, illnesses, and accidents) as well as to bring out interpersonal relationships (parents, parent to child, environmental, school). The examination of the child entails a searching physical examination stressing aberrations of anthropometric measurements, glandular dyscrasias, evidences of avitaminosis, allergic manifestations, confused laterality (mixed dominant handedness and

eyedness), and general part dysfunctions (visual and auditory defects, neurological disturbances). Psychometric studies are an essential part of the personality evaluation in order that we may know clearly the place the intelligence, not only absolute level but components as affected by physical part-dysfunction, has in the problem. Finally the child is given the opportunity to give his personal version of his difficulties; the child is alone with the examiner as is the informing parent when she or he is launching the diatribe about the child's maladjustment. This preliminary investigation is the base of the pyramid upon which the cascading evidence from social service workers, school reports, audiograms, ophthalmograms, electroencephalograms, the clinical laboratory, and detailed psychometric and personality investigation methods will finally accumulate toward the final answer—"What constitutes this particular personality organization and why is it functioning the way it is?"

The *general overactivity* of the hyperkinetic child serves to separate him to a great extent from the larger, almost all-inclusive group mentioned by Dr. Ira Wile in his editorial in *The Nervous Child*[9]—"Who is the Nervous Child?" In this comprehensive review are asked many pertinent questions regarding emotional integration and interrelationship. In the present study the main emphasis is upon evaluating physical abnormalities as they contribute directly or in the greatest part to the total maladjustment.

Since the educator, pediatrician, and general practitioner want to know "what to do" with these children after the diagnosis has been made, such conditions often associated with hyperkinesia as the severe mentally retarded cases, the microcephalics, and heredodegenerative diseases have been omitted. These are all too well known to the neuropsychiatrist and administrator of the state institutions and nonspecialized private boarding schools. In all of the following illustrative cases the patients have had average to superior intelligence and often have an expectancy of higher tested intelligence when the offending physical defects have been alleviated. In each case history the physical defect is studied as it furnishes the dynamics for maladjustment; a brief evaluation of the psychobiologic make-up is summarized; treatment course and adjustment are indicated.

PHYSICAL ABNORMALITIES CONTRIBUTING TO HYPERKINETIC BEHAVIOR

A. *Part Dysfunction*
- a. *Visual*
- b. *Auditory*
- c. *Speech*
- d. *Laterality*
- e. *Neurological*

B. *Systemic*
- a. *Allergy*
- b. *Endocrine*

A. *Part Dysfunction.*—

a. *Visual:* The educator is not so much interested in the child whose vision has been so greatly reduced that this child must be assigned to the "Sight Saving Class." Adequate educational provision has been made for these children. They are recognized early in the school program of physical examinations or in the well-organized preschool. The educator and parent becomes aroused when the average child enters second and sometimes third grade and seems to have "trouble with reading." Often the child has been able to "read" in first grade quite satisfactorily but is now "making no effort" to grasp the more difficult reading (where there are no pictures to guide him in his memory of the story his mother has read him). He becomes an irritable,

inattentive, restless, disturbing, and maladjusted child in contrast to the affable, complying child he had been. Often the teacher gets a report from the school nurse that the child's vision tested with the Snellen chart is 6/6, "normal." Somewhat later the school psychologist finds an average or better intelligence but likewise finds word reversals ("was" for "saw"), number reversals ("6" for "9"), mirror writing, mixed-up eyedness, handedness and footedness. The psychologist may employ further tests to determine whether there is binocular vision, eye muscle imbalance, good or poor near fusion during accommodation. Greater diagnostic accuracy is reached in determining ocular acuity and dynamic usefulness by watching how the child reads or photographing the eye movements (demonstration of vertical imbalance, limitation of scanning, regressions by the ophthalmograph). The psychologist will furnish more detailed material to the remedial reading teacher about visual imagery.[10] The ophthalmologists have pointed out that a seemingly minor handicap of hyperopia plus astigmatism (not readily revealed by the casual use of the Snellen chart) will cause much difficulty to a child who has this problem of a specific reading disability; they will also show that many children who are right-handed and -footed but left eye dominant will have difficulty in learning reading and writing easily. Often the pediatrician is given a clue to a refractive error in this otherwise right-sided child when the child places the "telescope" to the left eye or sights his imaginary gun with his left eye. A refractive error of greater severity in the right eye may be forcing this left-eyedness. Further comprehensive testing procedures have been described by another contributor to these Woods Schools conferences.[11] The pediatrician's concern with the problem of strephosymbolia (mixed symbols and laterality as related to specific reading disabilities) is stressed in Dr. Wyckoff's personal article[12] presented before the American Academy of Pediatrics in 1942.

CASE 1.—N. N., a white girl 7½ years old, was referred for examination by the private pediatrician because she was not making an adequate adjustment in a private school where she was considered "queer" by the children and parents. After two years' attendance, the school was insisting on removal. "Queerness" was described by the headmistress as an unusual hyperkinetic type of behavior: "She would wander around the schoolroom, go into drawers in desks or into strangers' houses, demand individual attention from the teacher even in a small class of ten pupils."

A clue to the problem was given early in the history by the mother. Reading had been a problem from the beginning. Even though remedial reading was being given in school, the girl still made word, letter, and number reversals. A physical defect noted by the parents was that her eyes had been straight at birth but in the last two years an upward, outward deviation of the left eye was slowly developing. Unfortunately this was a defect of the dominant left eye. She was otherwise right-sided. One ophthalmologist had advised against glasses.

The direct examination revealed a distractible, flighty, uncertain, restless girl whose Revised Stanford-Binet, Form L, revealed an I. Q. of 118. Spatial imagery and drawing of the designs were decidedly faulty. Auditory recall was superior to visual recall. Clinical reading tests were passed only at the first grade level. Occasionally she would cover her left eye while reading or drawing.

Treatment was begun with advising the immediate reinvestigation of the ocular status by an ophthalmologist thoroughly conversant with the problem of ocularity as related to reading problems. His report revealed: "This girl has a marked muscle error which might well be the basis of her entire difficulty. She has 18 degrees of exophoria for distance and 27 degrees exophoria for near with 4 degrees of right hyperphoria . . . the refractive error was practically nil." Muscle resection was followed after a prescribed period by remedial reading work. Final step toward the gradual, slow period of readjustment of this girl was to place her in the regular public school, where she would not be outstanding in the group because of her reading difficulties. When acceptance by the group progressed

as well as increasing reading skill, and self-confidence became established, this girl became progressively less the "queer," maladjusted, hyperkinetic, and unaccepted child.

b. *Auditory:* The paranoid, suspicious behavior of some adults with an auditory defect is well recognized by all those who have to associate with them. The child with a slowly progressing hearing loss, often due to recurrent middle ear infections, hypertrophied adenoids, or allergic rhinitis obstructing the pharyngeal opening of the eustachian tube, is most often given no benefit of the doubt by his parents or schoolteacher. He is called inattentive, often labeled the "daydreamer." He is a shy youngster, not well accepted by the group as he does not hear what is going on. The family may not be shocked into trying to find out what is wrong until he has failed once or twice, been brought to the Board of Education for psychologic tests, and possibly labeled "retarded." Congratulations to all those psychologists who have recognized the hearing defect at this stage and recommended audiometric examination. Parents and physicians also should give congratulations to the Boards of Education which provide special educational opportunities for the totally deaf: Braille and lip reading replacing the vintaged hand signal system, and then progress into hard of hearing classes as the child becomes facile enough to take his place in normal society. Unfortunately not all deafened children may be so effectively examined and dealt with as we have outlined. More often the vexed parent does not know there is anything physically wrong. The child is berated for his inattention and failure to obtain good marks or to pass. The child is driven. browbeaten, even physically beaten, and deprived of everything. The introverted child withdraws more. The extroverted child becomes agitated, fights back, and shows many of the symptoms accompanying hyperkinesia (tics, night terrors, truancy, enuresis, temper outbursts).

CASE 2.—E. E., a girl 12½ years old at the time of this writing, had been observed in the Child Psychiatric Clinic for eight years. The original complaints were: "extremely nervous, high-strung, unmanageable, strong-willed, violent when thwarted." It was difficult to reconcile the behavior of this girl during examination with the mother's tirades about her. E. E. was a patient, well-mannered, timid girl who lacked self-confidence. The Stanford-Binet was administered with reservations since the Otolaryngology Department advised that a partial nerve deafness (bilateral) was suspected; the intelligence quotient was 86.

Her course was a stormy one during these eight years. It was evident after two years in the small country school that her behavior was decidedly worse. Despite repeated efforts by the mother, the social worker, and the psychiatrist, the principal and teacher would not believe the relationship of the child's auditory difficulty and her failure to do good work. Inattentiveness was usually punished by placing the girl in the rear of the room where she *heard nothing*. From 8½ to 9½ years, the State Department of Education cooperated to the extent of sending her to a metropolitan school where special training for deaf children could be given. At the time of transfer the audiometer test revealed a high-frequency deafness with 100 decibel loss at the upper frequencies. Further psychologic tests revealed an educational age of 8 years, 8 months (chronological age 8 years, 5 months). The Arthur Point Performance test revealed a mental age of 10 years, 11 months with an I. Q. of 130. This performance test, in which verbal instructions are minimum as compared with the Stanford-Binet test, actually brought out the innate capacity E. E. had when uninfluenced by her extreme auditory handicap. Within a year she became proficient enough in lip reading to be returned to her regular school.

Despite several setbacks in school work because of teachers who would still not believe there was any auditory defect (despite the cold, objective figures of the repeated audiometer tests), she entered the eighth grade at 12½ years of age. There were no more emotional outbursts. She had gained enough self-confidence that she was not handicapped by her auditory defect in meeting either scholastic or social situations. This readjustment was well reflected in the constantly increasing tested intelligence quotient: as contrasted

with the first I. Q. of 86, the last Stanford-Binet, Form L, done in January, 1941, showed a mental age of 10 years, 4 months and an I. Q. of 116 If we had not carefully sought the underlying cause of this girl's behavior, rigorously directed physical treatment and closely supervised the interpretation of the physical disability as it affected the scholastic achievement, the ultimate outcome of the original hyperkinesia plus borderline intelligence might have been sadly different.

c. *Speech:* The hyperkinetic child with a disproportionate delay in speech development immediately presents a highly technical problem to the family physician or pediatrician. Many questions must be answered about mental capacity, physical defects, heredity, confused laterality, emotional conflicts. A carefully elicited history may clearly indicate the spoiled, only child with average or superior ability who gains his way and wants from overindulgent parents. Insistent grunts plus pointing are more economical to this child in obtaining his wishes. Should the desired object not be immediately given, this child becomes the frustrated child emphasizing his demands with wholehearted temper outbursts. Here is hyperkinetic behavior at its height: violent motor activity, head banging, shrill shrieking as good evidence of ability to vocalize, and there may be breath holding. He is frustrated in not getting what he wants and frustrated because he cannot verbalize. It is upsetting not to be able to make your wants known—in any language. The detailed study of this child may go outside the skill and knowledge of the general physician; but the physician can succeed through his intimate knowledge of the family and home constellation as interpersonal relationships may be contributing to the faulty language development; he also succeeds because he centrally controls what studies are being done and makes the final integration of these. He chooses the most competent otolaryngologist to determine the auditory status and structural abnormalities which can contribute. He refers to the psychologist who can most competently ascertain the intelligence level or general developmental quotient (Gesell) of this child whose very absence of speech makes such testing a job for only the astute clinician. Treatment depends upon the proper evaluation of all these studies. Training of the physically normal, intellectually adequate, but emotionally immature "only" child whom we have described, begins with the parents. The hyperkinesia of the intellectually retarded, but physically adequate child can often be reduced by having the parents give this child security—security achieved through accepting his slower advancement schedule and by not forcing him to live up to the achievement of the brighter nephews and nieces.

Speech defects other than this "delayed speech" necessarily contribute heavily toward children's maladjustments. The understanding of these defects is discussed in such a way by Kanner[6] and Karlin and Kennedy.[13] It should need no re-emphasis here that the total personality of the stammerer must be adequately studied and treated—treatment often calling for the closest teamwork of the speech therapist, physician, psychiatrist, psychologist, and social worker.

CASE 3.—L. K., a white girl, was 9 years old at the time of original investigation seven years ago. Stuttering had begun when she entered school at 5 years. Early developmental history was normal. She had always been entirely right-sided, though there was considerable left-sidedness in the family. In the family history was schizophrenia and another institutional case on the father's side. The father was a vindictive, paranoid, hotheaded alcoholic who made life miserable for his wife and children.

L. K. was basically a sensitive, meticulous, pedantic girl with superior intelligence. The first examination revealed not only the speech dysrhythmia, but also the underlying physical tension. During some attempts to speak she would grind her teeth and become

physically rigid while attempting to control the "m,m,m" or similar initial defect; there might be trismus of the jaw, general motor restlessness, increased heart rate, and knee jerks. At home the mother and father both goaded the girl to stop her "damn stuttering"; the younger children teased her until sometimes she would "become blue in the face and burst out hysterically crying."

Treatment had to be as varied as there were facets to the problem. Psychotherapy was directed toward alleviating some of the underlying fears (of Negro children in the neighborhood, carsickness); the family welfare agency had to carry on treatment with the parents until eventually the unstable father had to be excluded from the home. Until this was done, L. K. consistently showed such a poor advance on the Wetzel[14] Grid that physical rehabilitation had to be carried on at Children's Fresh Air Camp. Remedial speech therapy was carried on by a private therapist, a spasmodic affair because of the girl's own perfectionistic, compulsive (Rorschach-determined) demands for immediate results and the mother's resentful attitude that she must "do anything special" for the girl. When L. K. was 14½ years old the therapist wrote, "She still has some difficulty but it is practically negligible." He also had noted that with increasing speech improvement, the former hyperkinesia gradually lessened and disappeared.

d. *Laterality:* In these case discussions there has been mentioned something about the particular dominant handedness, footedness, or eyedness. Fortunately educators and parents have become more and more aware of the unfortunate aftereffects of forcing unnatural handedness: usually right-handedness in a child otherwise left-sided. Theoretically no harm may be done some children; clinically we wonder whether the forced change may not have had some causal connection with a delay in language development, or the appearance of a stutter in early school life, or with the over-all clumsiness of the child. Orton[15] described this "abnormal clumsiness" under the term "developmental apraxia." Parents should realize this neurological entity in the child who may be delayed in walking, who is slower in learning to feed and dress himself, who is so clumsy that simple sports are mastered only with the greatest difficulty. Great emotional tension can be avoided with all the concomitant sequelae if the parents do recognize this pattern of confused laterality and clumsiness and do not force the child beyond his maturational level of ability. The hyperkinesia of the child with confused laterality is well illustrated by the following case.

Case 4.—M. K., an adopted boy, was 3¼ years old at the time of the first examination in March, 1944. The private nursery school referred the boy because he was unusually slow in adapting to the group activities and because of unusual clumsiness. His adopting mother brought out that: he "doesn't coordinate properly"; he handled things like a little baby; his posture and gait were quite poor until special high shoes were obtained. Clumsiness and running into things may have been accentuated by his eye trouble, one eye had turned in since birth. When frustrated through his own inability to accomplish motor acts as quickly as others in the group or as parents expected, he had prolonged temper tantrums. Feeding and dressing himself were exceedingly difficult problems.

The physical examination revealed a thoroughly confused laterality. During accommodation he might use either left or right eye dominantly but good near fusion was present. (Subsequent refraction revealed a "considerable myopic astigmatism with preference for left-eyed dominance following refraction.") He was right-footed but ambidextrous. His gait and use of feet during play well illustrated his clumsiness. Bead-stringing, block-building, and crayoning demonstrated the poor coordination of manual activity. Despite all this confusion he was still able to obtain an I. Q. of 87 on the Stanford-Binet, Form L, psychometric test. Distractibility, overactivity, and impulsivity were apparent during the examination.

The family and school were both advised to allow natural maturation to take place with this boy. He must be allowed to establish his own dominance. Probably former pressure at home will continue to cause right-handed eating. At school, however, free choice of handedness with larger objects was allowed. Orthopedic supervision of shoe choice, ocular

study and correction, and psychiatric removal of environmental pressure combined to effect already a better emotional adjustment of the boy. Parents and teachers do much better when they have an understanding of any child's disabilities and capacities.

e. *Neurological:* Unfortunately it must be said that most school administrators do not welcome the child with any form of convulsive disorder. The doctor must assiduously evaluate history, clinical, and laboratory data before stigmatizing any child with the diagnostic tag "epilepsy." Mention has been made of Ford's[2] elaborate description of the postencephalitic and posttraumatic behavior disorders. The physician should clearly differentiate these and allied behavior disorders due to cerebral dysrhythmias (abnormal electroencephalograms) from the epilepsies. We are familiar with the impulsivity, the aggressiveness, emotional instability, temper tantrums, lack of concentration and judgment, the unpredictable explosiveness of these children who belong to either the posttraumatic or postencephalitic behavior group. Jenkins and Pacella[16] made a strong plea for this group of the "handicapped personality," stressing the need for special school programs. These are often the children with short attention span, inability to concentrate and to "adapt to a program of highly restricted activity and sedentary study." Those of us who are daily dealing with school maladjustments should be interested in a paragraph from these authors' conclusions: "School maladjustment resulting from failure to recognize and provide for such handicaps results in classroom rebellion or truancy, and puts the child in a position where delinquent influences are likely to play upon him and he is emotionally responsive to the suggestions of other delinquents who are maladjusted in school or who truant." They have found that this group has very frequently abnormal electroencephalograms. We, thus, have a convenient method for studying these problems: a method of separating on an objective, laboratory basis these cases which were puzzling in the absence of positive neurological findings and in the presence of relatively normal intelligence quotients. These are the children who may well profit from the special public school program described by Blau and Veo.[7]

Dr. Charles Bradley has studied these children with behavior of the "organic reaction type" at the Emma Pendleton Bradley Home in Providence. His report on "Problem Children: Electroencephalographic Diagnosis and Pharmacological Treatment"[17] is one of many* which have originated from this institution where children's behavior problems are intensively studied. This article suggested the use of benzedrene sulfate† in the following boy presenting severe school maladjustment.

CASE 5.—M. D., a 13½-year-old white boy, had been threatened with school expulsion for the past five years. Four months before psychiatric examination in December, 1939, he had fallen four feet on to a cement floor with minor traumatism of the forehead and a brief five-minute period of unconsciousness. Always having been a "nervous" child, it was difficult for the mother to clearly describe how much "more nervous and rowdyish" he had become. A diagnosis of "problem child" had been made in our outpatient department at 2 years of age. He had been destructive, belligerent, thoroughly disliked in the neighborhood. Four months following the accident he had a series of four, mildly severe, generalized convulsions over a period of three months. In school he lacked attention and concentration, showed poor judgment, was extremely aggressive and "bullying"; when angered, he had violent temper outbursts.

M. D. was one of seven children in a family which gave no history of cerebral dysrhythmias. The immediately preceding sister had died in an institution for the feeble-

*See Donald B. Lindsley's chapter on "Electroencephalography," Personality and Behavior Disorders, New York, 1944, The Ronald Press Co., Vol. 2, for comprehensive bibliography on electroencephalography.

†Racemic amphetamine sulfate: Smith, Kline and French Laboratories, Philadelphia, Pa.

minded from pneumonia; her retardation had been definitely caused by a cerebral birth injury. M. D.'s original Stanford-Binet, Old Form, in December, 1939, showed an I. Q. of 84; that this was affected by his specific disability in reading and arithmetic was well shown by a retest three years later when an I. Q. of 99 was obtained. Detailed hospital investigation was done in February, 1940, to determine whether there was any laboratory evidence of cerebral damage or any other physical abnormalities contributing to the boy's hyperkinesia. Overactivity, noisiness, and vacillating degrees of cooperation characterized the hospital stay which revealed primarily a severe degree of allergic sensitivity to inhalants. Because of the known correlation (to be discussed later) of hyperkinesia and allergic sensitivity in some cases, desensitization was begun in the allergy clinic. The effect was negligible in this boy. Combinations of various sedative and anticonvulsant drugs were given with minimal lasting effects.

In September, 1942, heroic measures had to be instituted because of the exacerbation of the hyperkinesia which affected his school adjustment and the adjustment of the "other 1,400 children in the school," as the principal informed me in exasperation. She was positive that it was all due to poor management in the home. The behavior was akin to what is seen in the mild posttraumatic behavior type.

Following Bradley's suggestions, benzedrene sulfate was administered in dosages finally amounting to 30 mg. a day. The dramatic improvement in adjustment warranted the procedure. School grades began to mount, attention span was definitely prolonged, the behavior was so dramatically changed that it was a pleasure to have him come to the dispensary for the necessary close physical checks. Only a minimal loss of weight was observed and no untoward interference with sleep was noted. Treatment was discontinued after four months. Adjustment continued with a mild exacerbation in September, 1943, which was again controlled by repeating the course of benzedrene sulfate. Electroencephalographic studies done in February, 1944, revealed a mild paroxysmal dysrhythmia of a generalized nature. There was no evidence of localized cortical lesion. It became advisable to change to sodium dilantin, but the adjustment continued in the home, school, and locality. M. D. already has shown such baseball prowess that he may well become a junior member of one of our major baseball leagues. Possibly his particular personality make-up will make him outstandingly competent in this vocation.

B. *Systemic.*—

a. *Allergy:* It is possible that too little attention is given by the general physician and pediatrician to the role of allergy in either causing or accentuating emotional disturbances. The allergist who is weekly treating these hyperallergic children is intimately aware of the asthmatic child's fear of the nocturnal attack of asthma; he may unhappily observe the insidious "fear of death" develop in these children who have a hypochondriacal personality make-up. He may look forward with foreboding to the "allergy season" with its concomitant increasing irritability and restlessness, the poorer school adjustment, the parental anxiety over the child's weight loss.

The diversity of nervous manifestations which have some allergic sensitivity as a basis was indicated by Winkelman and Moore:[18] "Certain of the cases at first glance seemed to be due to brain tumor, vascular lesions, or other gross organic defects." Stokes and Beerman[19] pointed out the way for greater clarification of this psychosomatic problem when they suggested a greater "liaison effort between dermatologic and psychiatric clinics." Karnosh[20] clearly expressed the complexity of the problem and the multiplexity of emotional, mental, and neural phenomena which are interlocked with the allergic reaction in human tissues. He stated in his introduction to "The Psychosomatic Aspects of Allergy" at the 1943 Forum of Allergy: "It becomes more and more apparent that this reaction involves every level of the nervous system from the highest and most elaborate centers of the cortex to the humblest sympathetic terminal in the capillary loop of the skin." Clarke[21] has continued his research and emphasis on central nervous system manifestations of allergy for over eleven years. He summarized his views in the 1944 Instruc-

tional Course for the American College of Allergists. Discussed by him are disease entities closely associated with allergic manifestations which have particular interest to the pediatrician and psychiatrist: cyclic vomiting, infantile convulsions, violent temper tantrums, petit mal, and occasionally grand mal seizures. Mild abdominal pains, headaches, inattention, and unruliness have been noted in school children by one pediatrician-school doctor; removal of wheat and "chocolate milk" from the diet of these elementary school children brought about an alleviation of symptoms in an unusual number of the children in from three to six months' time. Teachers also noted increased attention, decreased disagreeableness and restlessness, and a gradual increase in scholastic achievement. Clarke further reported the case of the surly, disobedient, wilful 13-year-old boy who had been expelled from four schools as incorrigible. Allergy studies revealed sensitivity to several foods as well as fall pollens. Removal of offending foods and desensitization resulted in a favorable, satisfactory readjustment of this seriously maladjusted boy.

CASE 6.—J. B. This 10-year-old girl offered the interesting problem of the truly hyperkinetic child who starts out life with the difficult feeding problem of pylorospasm. She had immediately shown such "signs of nervousness in the hospital that the pediatrician pronounced her a hypertonic child." Tomato and orange juice could not be tolerated. An extremely alert and active baby, she learned quickly and developed rapidly. Because of excessive activity, at times almost amounting to wildness, she was placed in a nursery school at 2½ years. Inability to go to sleep until late at night appeared. Her hyperkinetic drive was so disrupting to the whole home that she was placed in a boarding school for six months at the age of 8½ years. The recurrence of this uncontrolled behavior led to her hospitalization for complete physical study at 9¼ years. The essential abnormality of the investigation was in the realm of the allergist: orris root, 1 plus; mixed grass pollens, 2 plus; house dust, 3 plus.

Psychiatric examination showed a girl whose drive, distractibility, and hyperkinesia were such that she nearly climbed all over the examining room. The Revised Stanford-Binet, Form L, revealed a mental age of 12 years, 10 months and an I. Q. of 139. Impulsiveness, flightiness of thought, lack of application were apparent during this examination. The Rorschach test also verified this hypomanicism as it disclosed the egocentricity, emotional lability, and forceful drive.

Within three months after allergic desensitization had been begun, there had been such an amelioration of the child's behavior that the mother and father were unable to believe this was the same girl. The schoolteacher had also noted such a remarkable change in school that she asked what was being done for the girl. The repeat Rorschach examination eight months later disclosed much less explosiveness and drive; it indicated an increased maturity and better application of intelligence. Direct observation of the girl bore out the considerable decrease in hyperkinesia; she was not the "caged tiger" she had been at the time of original examination.

b. *Endocrine:* The possibility of some endocrine abnormality may be overlooked when the child presents a hyperkinetic type of behavior. We more often consider the child with some glandular deficiency as a dull, lethargic, phlegmatic individual. The mere mention of hypothyroidism conjures up a mental picture of an apathetic, dumpy dwarf with a mouth-filling tongue lolling out of the drooping mouth. When we speak of the Fröhlich syndrome, we think of a compliant, reticent, somewhat slow child who does not mingle in group activities. The fact cannot be overlooked, however, that the apprehensive, introverted, obese, or malnourished child may turn the tables in self-preservation and become "Peck's Bad Boy," and the school bully and terror. In like manner, the ordinarily placid, unruffled, docile child with an endocrine imbalance may overcompensate his personality defect and behave in the aggressive, hyperkinetic, near delinquent pattern. Lurie[3] not only pointed out this mechanism in the earlier mentioned article, but he described a "clinical syndrome" which bears

repetition. He asserted that this triad of symptoms of extreme motor restlessness, destructiveness, and speech disturbance in the young child "almost always indicates a state of hypothyroidism." It is difficult to reconcile this incongruous behavior with our accustomed ideas about thyroid dysfunction until we have encountered this behavior disorder and watched the effect of treatment.

CASE 7.—D. K., an 8-year-old boy, was referred to the clinic because of annoying tics, easy excitability, nail biting, wildness to the point of destructivness, and poor school adjustment because of this behavior. Examination bore out the extreme hyperkinesia: rolling and twisting in his chair, banging his feet on the floor and his head on the chair, constant oral noises. A speech deficit more in keeping with "baby talk" was observed. Height-weight plotting on the Wetzel Grid indicated a physical retardation of nine months; this was further borne out by shorter span, lower measurement, and total height. The Stanford-Binet, Old Form, showed a mental age of 10 years, 2 months and an I. Q. of 125.

Since this clinical picture suggested the triad mentioned by Lurie, the endocrine evaluation was made. Osseous age was retarded twelve months below chronological age; the basal metabolism according to body surface was −18 per cent. Adequate thyroid dosages were administered. Over two and one-half years there was seen a favorable physical response to the therapy as well as decreased hyperkinesia and an improvement in speech.

SUMMARY

The "exceptional child" presents a challenge to the diagnostic acumen of every physician, psychologist, orthopsychiatrist, and educator who must contribute toward the satisfactory home and school adjustment of this child. An effort has been made in this paper to correlate material from diversified fields all interested in understanding and treating the behavior deviations of children. Emphasis has been placed upon physical abnormalities which directly or through their psychogenic implications affect the child's behavior to produce what is termed the "hyperkinetic child."

It is incumbent upon every physician to conscientiously evaluate the importance of these physical aberrations as they may or may not contribute to the children's behavior disorders. When the physician is satisfied that the sum of minor or major physical abnormalities does *not* constitute the etiology of the disorder, he should frankly search for psychogenic factors or refer to those physicians or agencies where examinations can be made to ascertain and deal understandingly with these features of conduct. He should not be among those who contribute to the "miscomprehensions of parents concerning child health and behavior"—a subject so recently studied and reported by Jacques[22] from the Harvard University Psychological Clinic.

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2103 ADELBERT ROAD

A SIMPLE DEVICE FOR TIMING PRECORDIAL MURMURS

MARTIN M. MALINER, M.D.
BROOKLYN, N. Y.

THE important considerations in the analysis of a cardiac murmur according to Cabot* are:

1. Its place in the cardiac cycle,
2. Its point of maximum intensity,
3. The area of transmission,
4. The effects of exercise, respiration, or change in posture.

This discussion concerns the first and most important thing to ascertain regarding a murmur, its relation to the normal cardiac cycle; that is, whether it occurs during systole or during diastole. This apparently is simple. One must merely bear in mind that the period of systole lasts from the beginning of the first sound up to the occurrence of the second sound, while diastole extends from the beginning of the second sound until the beginning of the first sound in the next cycle. However, everyone will admit that the commonest of all the errors in the diagnosis of valvular disease of the heart is to mistake systole for diastole and thereby misinterpret the significance of a murmur heard during those periods. The majority of physicians tend to trust their ability to appreciate cardiac rhythm to tell them which is the first heart sound and which is the second sound. This method is even unreliable to the experienced cardiologist; using the radial pulse as a guide is equally untrustworthy. The most acceptable methods for properly timing murmurs have been the use of a finger upon the apex impulse of the heart or on the neck over the carotid artery while listening for murmurs and occasionally in the thin chested individual by observing the impulse. More often than not, however, the impulse is neither seen nor felt and again proper timing is inaccurate. Appreciating the necessity for some simple measure for the proper timing of murmurs I frequently noticed an interesting phenomenon during the examination of female children in the cardiac clinic. Usually girls wear a locket or medallion of some sort suspended on a thin chain about the neck and when the locket was turned to the rear of the

From the Pediatric Cardiac Clinic of the Post Graduate Hospital and Medical School, Columbia University, New York.

*Cabot, Richard C.: Physical Diagnosis, New York, 1915, William Wood & Co.

neck in order to have a clear space for examination, that portion of the chain suspended in the triangle just above the suprasternal notch was seen to move up and down synchronously with the cardiac cycle; with systole the chain is elevated and with diastole it drops. After further observation, a few inexpensive chains from a local five and ten cent store were obtained and the experiment was applied to all children. The chain is lightly suspended about the

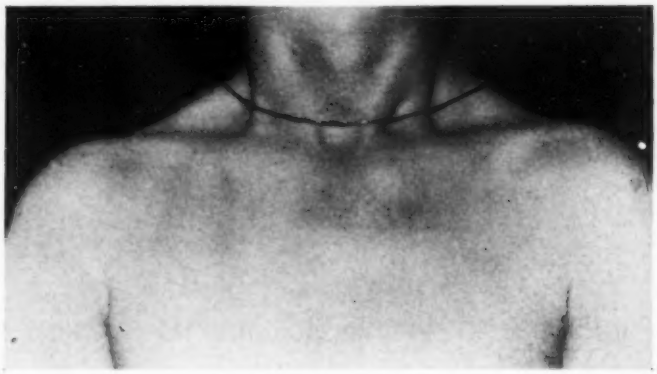

Fig. 1.

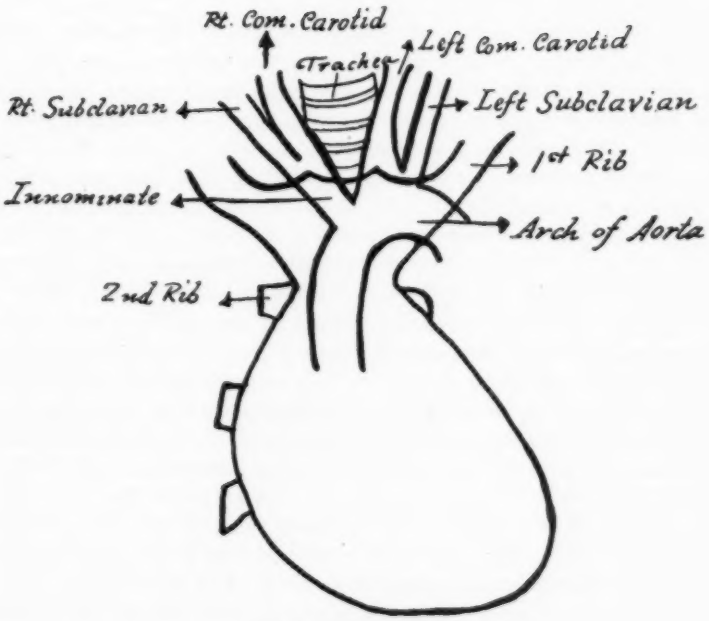

Fig. 2.—The aortic arch.

neck approximately one inch above the suprasternal notch and the patient is asked to elevate the chin a little in order to add tension to the muscles of the neck and so accentuate the concavity of the suprasternal notch (Fig. 1). In every child, male or female, cardiac or noncardiac, the necklace was raised or lowered according to the cardiac cycle. This offered a simple means of timing cardiac murmurs. Fig. 2 explains the factors involved. The arch of the aorta

actually rises to the level of the upper border of the first ribs, while the innominate, subclavian, and common carotid on the right side and the subclavian and common carotid on the left side course the neck. During systole the pulsations of these large vessels cause the neck to expand elevating the chain and during diastole the collapse of these vessels is associated with the dropping of the chain. These vessels are so proximal to the heart as to make the pulsations practically synchronous with the cardiac cycle and the timing of cardiac murmurs is accurate.

SUMMARY

A thin necklace chain lightly suspended about a patient's neck serves as an ideal method for accurately timing cardiac murmurs.

MECHANICAL SUFFOCATION DURING INFANCY

A Comment on its Relation to the Total Problem of Sudden Death

Paul V. Woolley, Jr., M.D., Portland, Ore.

ABRAMSON,[1] in a recent contribution, has brought to attention accidental mechanical suffocation as a cause of death during infancy and has pointed out the alarming frequency with which this diagnosis is made. He has stated that one hundred and thirty-nine babies were reported dead from suffocation during a five-year period in New York City alone. This is a larger number than the total for measles, scarlet fever, and diphtheria and is as striking as the earlier report of Gafafer[2] who found suffocation to account for over one-third of all accidental deaths in infants under 1 year of age. It is difficult to read a city newspaper over an extended period of time and not be impressed by the frequency with which infants appear to be asphyxiated in their beds.

There is no doubt as to the seriousness of the problem but we wonder whether emphasis is being placed at the right point; a distressingly large number of babies die without noticeable predisposing cause, but is the primary premise correct, that all reported as having suffocated actually died from simple occlusion of air passages by bedding, sleeping attire, or other mechanical means? A certain number are garroted by tightly fitting sleeping devices or are compressed by larger bedfellows but we are far from convinced that good evidence exists to support the theory that more infants suffocate than die from burns, trauma, foreign bodies, and automobile accidents combined.[2]

One of the most distressing features to be faced upon the death of a child is the invariable presence of self-incrimination and guilt on the part of the parents. This can be dispelled only through sincere assurance by the attending physician that all possible was done to avert the catastrophe and that the outcome could not have been altered through changes in their behavior. To leave the family with a clear conscience is a duty secondary in importance only to saving the patient, and the physician should take all measures to be able to do this; it is often the prime motive for a post-mortem examination. It is there-

From the Doernbecher Memorial Hospital Unit and the Department of Pediatrics, University of Oregon Medical School, Hospitals and Clinics.

fore in keeping that we should be overly critical of a diagnosis which saddles the family with the entire blame for the death of their baby; for having allowed him to smother.*

Just what evidence can be adduced for this belief that a large number of healthy infants die from suffocation? So far as we can determine from reading, talking to pathologists, and querying coroners, a large portion of it rests on folklore; upon such practices as keeping the cat off the bed for fear it might "steal the baby's breath." We find no record of anyone having observed an infant suffocate without benefit of patented sleeping devices or other mechanical aids, nor can we find work which might suggest that anoxemia has been experimentally produced through arrangements of the usual bedding in relation to a normal baby. Certainly there is nothing pathognomonic of suffocation to be seen at autopsy; a few petechial hemorrhages scattered over the pleura and reflecting at most an increased vascular permeability during extremis. Our everyday experiences, such as the difficulty of maintaining high oxygen concentration in fabric tents constructed for this purpose, certainly do not lead to a belief that flimsy bedclothes would be an effective deterrant to free gaseous diffusion.

Some time ago, in association with Dr. Robert McCammon, we analysed the atmosphere breathed by infants covered in various manners by different types of bedding. We were able to demonstrate a reduction in oxygen or increase in carbon dioxide only after the addition of a rubber sheet, secured tightly at each border. The infants under ordinary bedding showed no discomfort until sufficient time had elapsed for heat and humidity to come into play. We also attempted to induce anoxemia by having the subjects sleep with nose and mouth closely approximated to mattresses and pillows but here again we were unsuccessful since the smallest was capable of rolling to obtain an airway and the larger were generally out of accord with the position.

Several points in the various compilations of case reports also are not in agreement with what we would expect were suffocation the entire story. For instance, Gafafer found the highest incidence not in the northern tier of states where bedding is at a maximum for the longest season but in the negroes of the south; New England, in fact, had the lowest rate. Abramson's finding that the peak is during the winter months is irrelevent in this respect since it might as well be correlated with the incidence of respiratory infections as the amount of bedding. Likewise the greater frequency in the economically less fortunate groups probably hooks up as well with crowding and poor living standards as with the possibility of mechanical compression since the same writer found evidence of overlaying in only a few instances. The mean age of 3 months for Abramson's cases would appear to be a little old if plain mechanical suffocation is to explain the picture since the 3- and 4- month baby is certainly robust enough to express vocally his views on other causes of discomfort and would, on the surface at least, be a less likely victim than a younger infant.

If we are led to doubt the importance of suffocation as an explanation of sudden death in sleeping infants, what other hypotheses can be substituted? The thymus has ceased to be popular although we would prefer it to suffocation; it implied no negligence nor did it infer that death was avoidable. In general, three groups of possibilities deserve consideration whenever the cause of death

*The implication of negligence when an infant dies from "suffocation" is so thoroughly ingrained that Templeman,[2] expressing the enlightened social outlook of the 1890's, suggested criminal prosecution of parents as one method of control. This despite the statement that, "Most of these cases occur in one-roomed houses, where frequently father, mother, and two, three, or even as many as five children sleep in one bed, which sometimes consists of a few jute sacks spread out on the floor."

in an infant is not obvious and regardless of whether the event occurred while asleep or awake. The first is infection by a variety of pathogens, the second is congenital anomalies, and the third might be called physiologic dysfunction.

Farber[4] was one of the first to emphasize overwhelming streptococcic septicemia in the etiology of unexpected death and recently we have seen two instances of meningococcemia terminate a matter of hours after the first symptom. The cause of death in one of these patients was not clear even at autopsy and was elicited only through a positive blood culture. A large part of our clinical evidence of infection is due to reactions by the body against the insulting agent, not to the presence of the organism per se, and it is of interest to speculate on the likelihood of rapid and relatively asymptomatic deterioration from septicemia in individuals virginal so far as previous conditioning of reaction is concerned. Topley[5] points out much the same problem in discussing local response to invasion. The various neurotropic viruses hold great theoretic potentiality as producers of sudden death because of their predilection for small cell collections essential to life. They notoriously produce little gross change which would be recognized during most post-mortem examinations. Goldbloom and Wiglesworth[6] have stressed the frequency with which they encountered a diffuse pneumonic process following unexplained death, but this might be another manifestation of an overwhelming septicemia rather than the actual cause of death; much the same relationship as exists between acute tracheobronchitis and the collapse which often accompanies it.

Congenital anomalies at a variety of strategic sites are capable of giving rise to sudden organic failure and death. The acyanotic type of cardiac defects may go along without recognition until the infant, through increasing body bulk and activity, provides a load sufficient to produce decompensation. Eight examples of this sequence have been presented by Levinson.[7] Rupture of congenital aneurysms, situated in such important areas as the base of the brain, can produce fatality as rapidly as can vascular accidents in older age groups, where the term suffocation is rarely used to explain the event. Mild degrees of laryngeal obstruction, sufficient to cause only periodic stridor during normal health, may be of extreme importance when edema from an otherwise mild respiratory infection is superimposed.

Physiologic dysfunction, while less clearly definable than the preceding categories, is one where speculation might prove most fruitful. The rapid growth, so characteristic of the early months, results in constant change of physiologic relationship and in gross instabilities; the exaggerated pyrexia in seemingly unimportant infections, the ease with which normal fluid and electrolyte interplay deteriorates during periods of minimal insult, the notoriously poor tolerance to surgery and anesthesia, and the rapidity with which vitamin deficiencies become manifest, are all reflections of the stage of disequilibrium. There must be a variety of these functional patterns capable of leading to sudden death. For example, hyperplasia of the isles of Langhans was the principal finding in a recently reported instance[6]—how often would hypoglycemia be detected clinically in the age group and how often is a careful microscopic study made routinely of the pancreas? Another writer,[8] in an attempt to explain anesthetic deaths, has postulated a development stage in infancy during which the respiratory center is markedly unstable to minimal changes in oxygen and carbon dioxide tension; possibly some such mechanism is of general importance.

These are by no means complete lists of the causes of sudden death in infancy but they illustrate some of the conditions to be considered before resort to suffocation. We, as pediatricians, should take the the lead in being a little more critical of the diagnosis and should reserve it for instances when actual deprivation of oxygen by mechanical means can be proved. Complete autopsy examination with full recourse to modern bacteriologic techniques should be demanded in every unexplained death of an infant. When this is done and still nothing is found, nor has incontrovertible evidence of suffocation been elicited, perhaps we should be pushed so far as to admit that we are ignorant of the cause of death, thereby saving the family the stigma of having allowed their baby to smother in the bedclothes. Status thymicolymphaticus or generalized incompatibility with life are more merciful and no more out of accord with the facts now available. We are heartily in accord with Dr. Abramson's belief that attention should be directed to the exceedingly large number of deaths which occur in supposedly healthy infants but we feel that further evidence is necessary before accounting the entire picture to mechanical suffocation.

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THE TREATMENT OF RHEUMATIC FEVER WITH PENICILLIN

LOWELL A. RANTZ, M.D., WESLEY W. SPINK, M.D., PAUL BOISVERT, M.D.,
AND CAPTAIN HOWARD COGGESHALL, MEDICAL CORPS,
ARMY OF THE UNITED STATES

PENICILLIN has been used successfully in the treatment of a variety of infections, nearly all of which have been those caused by the pyogenic cocci. Its value in the management of certain other diseases, either definitely or probably of infectious nature, has not been determined. Rheumatic fever is one of these.*

This serious disorder involves many tissues and organs, among which the heart and joints are most important. Considerable evidence exists which indicates a close etiological relationship between infection by the hemolytic streptococcus and the development of rheumatic fever. It appeared possible, therefore, that penicillin might be useful in the treatment of this disorder, since it favorably affects the course of most infections caused by these organisms. On the other hand, the sulfonamides are known to affect favorably the clinical course of hemolytic streptococcic infections, but these drugs are now considered to be definitely contraindicated in the treatment of patients with acute rheumatic fever.

It has recently been possible to treat six young male adults suffering from typical rheumatic fever with penicillin. Salicylates were withheld in every case but one until the efficacy of the antibiotic had been evaluated. Penicillin was administered intramuscularly at four hourly intervals, appropriately diluted in sterile normal salt solution. In addition, cultures of the nose and throat were performed in the usual manner, before, during, and after penicillin therapy. Hemolytic streptococci isolated each time were grouped and typed by the precipitin techniques of Lancefield. Immunologic studies were carried out on the sera obtained at frequent intervals from the patients, and the results of these observations will be recorded in another report. Leucocyte counts of the blood of the patients were determined at least twice a week. A series of sedimentation rates of the erythrocytes were carried out at appropriate intervals, utilizing the Westergren technique. Serial electrocardiograms recorded during the illness of each patient were also obtained.

RESULTS

CASE 1 (E. R., aged 23).—This patient was admitted to the hospital with a history of upper respiratory infection with sore throat for several days. Shortly after entry he developed acute pain in both knees and the right middle finger. Fever to 102° F. appeared and the arthritis

This investigation was conducted during a field study by the Commission on Hemolytic Streptococcus Infections, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Division, Office of the Surgeon General, United States Army.

The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

*Since this manuscript was completed, two reports on the use of penicillin in rheumatic fever have appeared. 1. Watson, R. F., Rothbard, S., and Swift, H. F.: J. A. M. A. 126: 274, 1944. 2. Foster, F. P., McEachern, G. C., Miller, J. H., Bail, F. E., Higley, C. S., and Warren, H. A.: J. A. M. A. 126: 281, 1944.

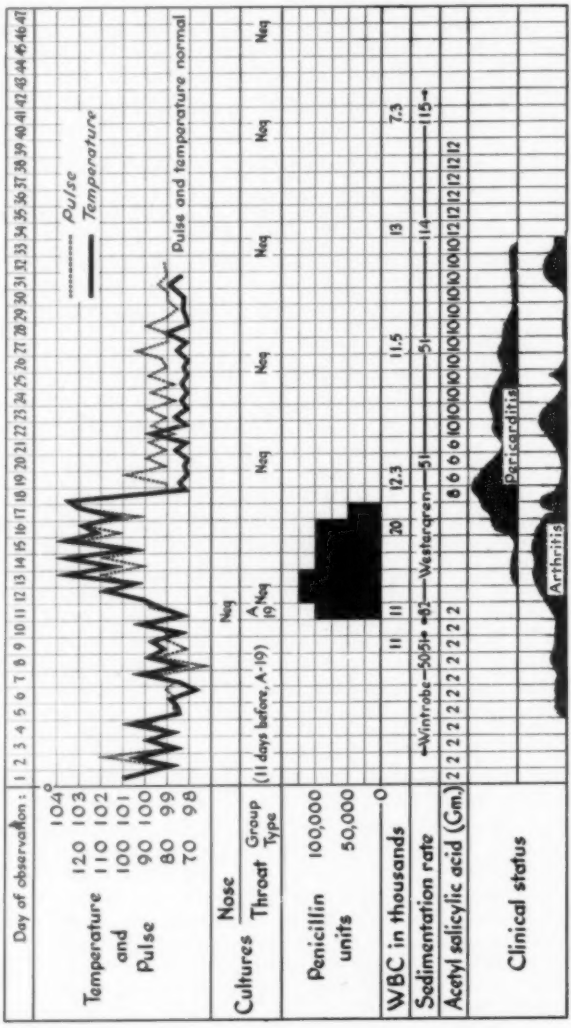
extended to other joints. Physical examination revealed painful knees and swelling of the midphalangeal joint of the right third finger, and a normal heart. A P-R interval of .24 seconds was demonstrated by electrocardiography. The leucocyte count was 9,000 per cubic millimeter and the erythrocyte sedimentation rate, 35 mm. per hour. Group A, types 19 and 3, hemolytic streptococci were recovered from the pharynx and type 5 from the nose. Penicillin therapy was instituted on the third hospital day and he received 1,000,000 units in nine days. Coincident with the exhibition of the agent the temperature returned to normal, and the arthritis disappeared. Within ten days after the conclusion of treatment the erythrocyte sedimentation rate was approximately normal. He progressed to an uneventful recovery. Hemolytic streptococci of the initial type disappeared from the throat during therapy, but organisms of type 19 were subsequently isolated. This may have been an instance of reinfection.

CASE 2 (J. B., aged 22).—This patient was admitted to the hospital with a history of polyarthritis for five days. He had had a sore throat two weeks before admission. The disease began with pain and swelling of the knees, followed by the involvement of the right wrist. On examination, the temperature was elevated to 102° F., the knees were swollen, hot, and contained fluid; the right wrist was swollen and warm; and the heart was normal. The erythrocyte sedimentation rate was 80 mm. per hour; the leucocyte count, 16,300 per cubic millimeter; and the electrocardiogram revealed a P-R interval of .24 seconds. Group A, type 1, hemolytic streptococci were isolated from the nose and throat. During the first three hospital days he became more severely ill. The leucocyte count increased to 42,000 per cubic millimeter and a loud pericardial friction rub could be heard. Penicillin therapy was instituted at this time and he received 1,000,000 units over a period of ten days. During this time the temperature rapidly returned to normal, the joints improved and the evidence of pericarditis disappeared. Hemolytic streptococci of the initial type disappeared from the nose and throat and were not recovered again. It appeared that penicillin had favorably affected the course of the disease, but the erythrocyte sedimentation rate remained abnormal during a period of observation of over sixty days, and he continued to have moderate arthralgia. With the institution of salicylate therapy in a dose of 10 Gm. per day, the joints rapidly improved and the sedimentation rate returned to normal within three weeks.

CASE 3 (O. H., aged 29).—This patient was admitted to the hospital with a history of polyarthritis for one day. There was a history of a similar episode nine years before. Two weeks before entry he had suffered from a sore throat. On admission he was febrile and the right wrist was painful. The leucocyte count was 24,000 per cubic millimeter; the erythrocyte sedimentation rate, 55 mm. per hour; and the electrocardiogram was normal. Untypable Group A hemolytic streptococci were isolated from the throat. After hospitalization there was an increase in the number of joints involved, and they became more painful and swollen. Penicillin therapy was instituted and he received 1,000,000 units in eleven days. During treatment pericarditis appeared as evidenced by the development of a friction rub and characteristic changes in the electrocardiogram. This gradually subsided, the general condition improved, and the temperature became lower. However, he remained ill, with low-grade fever, rapid sedimentation rate, and moderate arthralgia for two weeks, at which time salicylates were administered. Following this he improved rapidly.

CASE 4 (A. F., aged 41).—The clinical course of this patient is shown in Fig. 1. He was admitted to the hospital with tonsillitis due to Group A, type 19, hemolytic streptococci. He recovered uneventfully

and was discharged from the hospital but returned seventeen days after the onset of the initial illness, complaining of fever and generalized aches. He received small doses of salicylates for a few days but developed pain in several joints. The leucocyte count was 11,000 per cubic millimeter; the erythrocyte sedimentation rate, 51 mm. per hour; and the electrocardiogram revealed a P-R interval of .36 seconds. Type 19 streptococci were still present in the throat. Salicylates were discontinued at this time and penicillin administered, and he received


Day of observation: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47
Temperature and Pulse
104°
103
102
101
100
99
98
120
110
100
90
80
70
Pulse
Temperature
Pulse and temperature normal
Cultures
Nose
Throat
Group Type
(11 days before, A-19)
A 19
Neg
Penicillin units
100,000
50,000
0
WBC in thousands
11
11
20
12.3
11.5
13
7.3
Sedimentation rate
Wintrobe—50
51
62
Westergren—51
114
115
Acetyl salicylic acid (Gm.)
2 2 2 2 2 2 2 2 2 2
6 6 6

and he remained ill. The initial type of hemolytic streptococcus disappeared from the throat during therapy and was not recovered again. Two months later he had not yet completely recovered.

CASE 5 (E. M., aged 28).—This patient contracted several upper respiratory infections due to hemolytic streptococci while he was convalescing in the hospital from a fracture of a vertebra. Multiple attacks of tonsillitis are recorded in Fig. 2. It is of interest that prior to the development of rheumatic fever the tonsillitis was treated both locally and parenterally with penicillin. The local administration of penicillin was without demonstrable therapeutic benefit. While the parenteral administration of penicillin appeared to help him, it did not prevent a subsequent attack of acute rheumatic fever. Ten days after the second episode of tonsillitis caused by hemolytic streptococci of Group A, types 19 and 3, the wrists, shoulders, ankles, and knees became painful and swollen, and the temperature was 102° F. The leucocyte count was 30,500 per cubic millimeter; the erythrocyte sedimentation rate, 55 mm. per hour; and the electrocardiogram was normal. Penicillin therapy was instituted and he received 900,000 units in six days. During this time the temperature remained elevated, the arthritis became more severe, and he developed a very marked tachycardia. Because he appeared to be failing, penicillin was discontinued and salicylate therapy instituted. This change in regime was associated with rapid improvement but his subsequent convalescence, after salicylate therapy had been discontinued, was complicated by a reactivation of the rheumatic process associated with a tonsillitis caused by streptococci of type 1. The initial type of hemolytic streptococcus disappeared during therapy and was not recovered again.

CASE 6 (R. S., aged 23).—This patient was admitted to the hospital with a history of polyarthritis of six days' duration. There was no past history of arthritis or of a sore throat. The knees were swollen and contained fluid, the left foot and right elbow were red and tender, and the heart was normal. The leucocyte count was 10,000 per cubic millimeter; the erythrocyte sedimentation rate, 56 mm. per hour; and the electrocardiogram was normal. Group A, type 36, hemolytic streptococci were isolated from the nose and throat. For two days his arthritis became more severe and penicillin therapy was insituted. He received 700,000 units in five days. During this time the temperature became progressively higher, a marked tachycardia developed, as well as the physical and electrocardiographic signs of pericarditis. After five days of penicillin therapy, heart failure appeared as characterized by dyspnea and cyanosis. Since his condition was very grave, penicillin was withdrawn and salicylates administered, following which he made a rapid and uneventful recovery. Hemolytic streptococci of the initial type disappeared during therapy and were not recovered again.

DISCUSSION

From a study of six cases it is not possible to evaluate completely the usefulness of penicillin in the treatment of a disease whose course is as variable as that of rheumatic fever. The results strongly suggest that it is not only of no value but also may be harmful.

Coincident with the use of penicillin in Case 1, the result would appear to be excellent, but this was an example of a mild form of the disease. The clinical course of the other five patients during penicillin therapy was poor. A second patient improved (Case 2), in that the temperature became normal and the pericarditis and arthritis decreased in intensity, but he did not recover during a period of observation of sixty days; his disease being then promptly terminated by the administration of

salicylates. The administration of penicillin was associated in the other four with a progressive increase in the severity of their disease. All remained febrile; in three, pericarditis appeared; and in two, heart failure became apparent. The sixth developed a severe tachycardia.

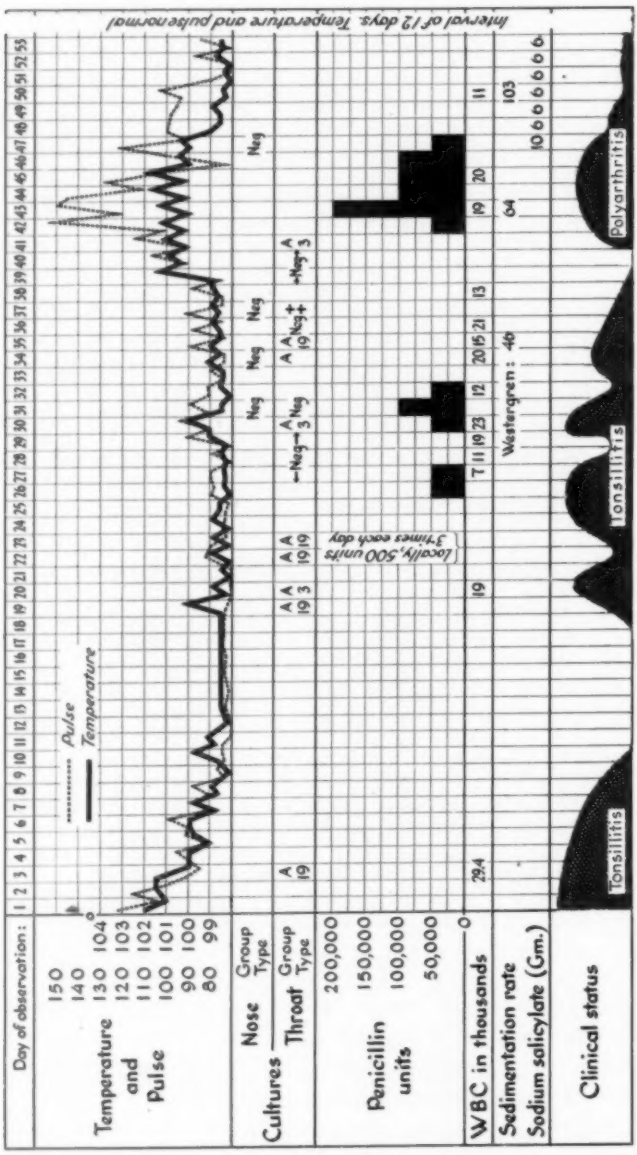


Fig. 24.

Fig. 2.—Clinical course of Case 5, male patient, aged 28 years, having acute rheumatic fever treated with penicillin. Note that polyarthritis increased in severity coincident with administration of penicillin, but improvement immediately followed salicylate therapy. (This chart is divided into two parts. See opposite page.)

In every case the alarming clinical state was rapidly controlled by the administration of salicylates. It is not clear whether four of these six individuals suffered initially from a severe rheumatic fever which progressed unchecked by salicylates, or whether their disease was aggravated by the administration of penicillin. If this small group be compared

with a much larger one treated conventionally during the same season, it seems very probable that the latter hypothesis is correct.

Interesting theoretical considerations are raised by the availability of an agent such as penicillin which is actively bactericidal for the hemolytic streptococcus and its application to the treatment of rheumatic fever. Although a close etiological relationship exists between infection, particularly of the pharynx and tonsils, by the hemolytic streptococcus

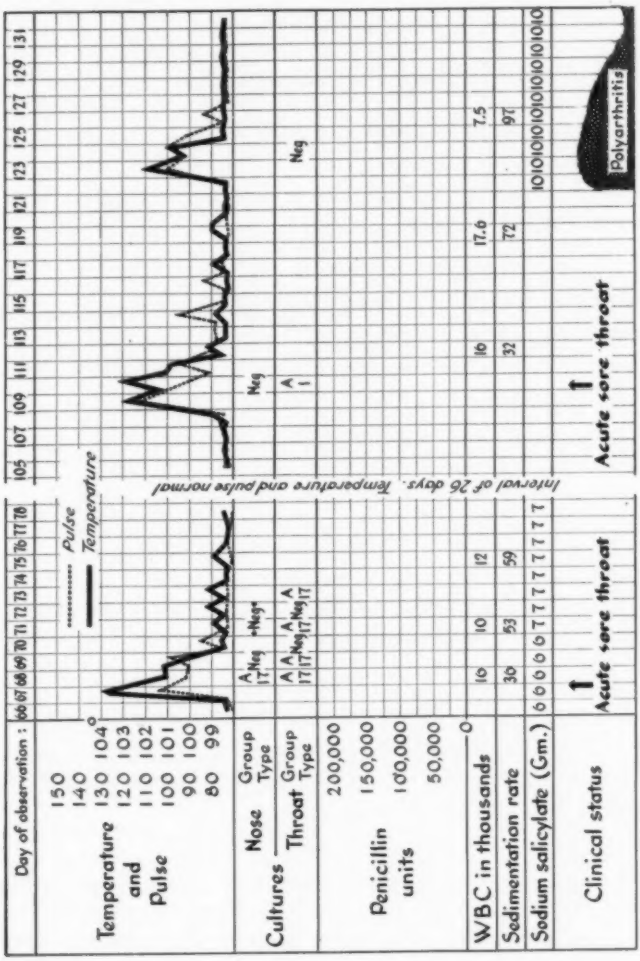


Fig. 2B.

of Group A, and the development of the rheumatic process, no convincing evidence has been presented which would demonstrate these organisms to be present in any of the affected tissues peripheral to the nasopharynx. It has, therefore, been necessary to postulate the development of sensitivity of the tissues to products of the streptococcus or to the appearance of an abnormal antibody response developed by the individual in response to infection with these organisms.

Penicillin, in the light of these facts, might not be expected to accomplish more in the rheumatic subject than the elimination of the causative

type of hemolytic streptococci from the tissues of the nasopharynx. This result was attained in every instance in this study. Had their presence been important to the continued activation of the disease, improvement should have followed this event. Its failure to do so strongly suggests that the hemolytic streptococcus carrier state is not related to the continuing rheumatic process.

One other possibility remains. The destruction of large numbers of hemolytic streptococci in the nasopharynx may have flooded the patient with unusual amounts of bacterial products and thus have been responsible for the severe clinical course observed in these patients. This possibility suggests that a clinical trial of penicillin therapy, adequate to eliminate the hemolytic streptococcus from the nasopharynx of rheumatic subjects who were fully protected by salicylates, may be in order. Since the clinical response to the salicylates is usually excellent, any advantage inherent in the use of penicillin could be determined only by the study of a large group with adequate controls.

SUMMARY

1. The administration of penicillin did not favorably affect the course of rheumatic fever in six individuals.

2. Group A hemolytic streptococci were eliminated from the nasopharynx in every case.

PENICILLIN TREATMENT OF ORAL INFLAMMATIONS IN CHILDHOOD

M. B. Marks, M.D.
Miami Beach, Fla.

THE three most common inflammations of the mouth in infancy and childhood are thrush, Plaut-Vincent's infection, and herpetic stomatitis.

THRUSH

Thrush is most commonly seen in the first two to three months of life and is characterized by small white flecks or larger patches on the cheeks and tongue which, when removed, cause pin-point hemorrhages. They should be differentiated from milk deposits which are easily wiped off. The organism causing the disease is the *Saccharomyces albicans*. It can easily be seen by removing some of the exudate and examining it on a slide with a drop of 10 per cent potassium hydroxide. Culture on Löffler's medium demonstrates the large spores of the Saccharomyces. Thrush characteristically gives very few subjective symptoms. The mouth is sometimes dry and local pain and tenderness are conspicuously absent.

The following case reports demonstrate the use of penicillin, both parenterally and topically, in rather severe cases of thrush:

Baby C., female infant, 2 months of age, was born six weeks prematurely. Her birth weight was 4 pounds, 1 ounce. Because of marked feebleness and poor temperature regulation mechanism, she had to be placed in an incubator. Shortly after birth, the baby developed thrush, which became severe. The entire soft palate, tongue, and the buccal mucosa bilaterally became involved with the tenacious, white flaky crust. Examination with 10 per cent potassium hydroxide established the diagnosis.

This condition of the mouth persisted for four weeks, despite the use of 1 and 2 per cent gentian violet, hydrogen peroxide swabbing, and boric acid irrigations. It was then decided to place the infant on penicillin therapy. Ten thousand units of penicillin were given intramuscularly every three hours until 40,000 units had been given. The result was dramatic. The lesions gradually regressed and in three to four days were practically gone.

Baby D., female infant, aged 3 months, was most probably infected by her older sister, aged four years, who had had a severe mouth infection two weeks before. The infant had lesions of the buccal lining, palate, and tongue, and particularly had a cluster of lesions under the tongue and above the floor of the mouth. Potassium hydroxide smear failed to demonstrate the lesions. The baby had been treated with gentian violet solution, hydrogen peroxide, and glycerite of boroglycerin with only slight improvement.

The mother was given a penicillin dilution of 250 units per c.c. and was instructed to apply the solution with swabs and loose cotton packing under the tongue and along the buccal surfaces every two hours. The topical use of the solution was gratifying. While the infection did not clear as rapidly as when the drug was injected intramuscularly, still the end result was as good. Improvement in the lesions began at once. At the end of a week the mouth was healed. This is an excellent example of the effects of the topical use of penicillin solution in the treatment of thrush.

PLAUT-VINCENT'S INFECTION

Under Plaut-Vincent's infection, we include all infections of the mouth which have as their etiology the spirochete Vincenti and the fusiform bacillus. Various synonyms have been applied to this condition, such as *trench mouth, ulcerative stomatitis, Vincent's angina,* and *ulcero-membranous tonsillitis.* The severe form of the disease is often seen following the so-called "virus" infections. The patient may show no symptoms for several days save high fever, or with the fever there may be a reddened throat with or without tonsillar involvement. Peculiarly enough, a sore throat is a rare complaint. Shortly after the onset of these symptoms, the physician discovers spongy, swollen, easily-bleeding gums. There may be friable, ulcerated areas on the surface of the tonsils when present. As a rule, there is a marked fetor oris.

V. H., 10-year-old female child, developed high fever and sore throat, together with a cough. She was placed on sulfonamide therapy with only slight improvement in her condition. On the fifth day of her illness she developed a severe Vincent's infection of her mouth and pharynx. The gums were very spongy and bled easily on touching them with the tongue depressor. The mucous membrane of the gums was so swollen that the crowns of the two rear upper molar teeth were almost

completely covered bilaterally. The anterior pillars in the pharynx were the seat of deep beefy-like ulcerations. There was a marked fetor oris. The child was unable to swallow comfortably and complained of severe pain when masticating her food.

She was given 20,000 units of penicillin intramuscularly every three hours until 100,000 units had been administered. The response to penicillin therapy was prompt. After forty-eight hours there was almost complete disappearance of the edema and the bleeding character of the gums. The deep ulcerations in the pharynvx did not clear for ninety-six hours. At this time the mouth was practically healed and the child was eating everything comfortably.

J. L., was a 3-year-old female. Her mother had treated her for trench mouth for about a week without any great improvement in the condition. The mouth infection came on after the child had apparently recovered from a "flu," which had lasted for four days with high fever, rhinitis, and a cough. On examination, the child had puffy, bleeding gums, together with an acute follicular tonsillitis. She had several ulcerations on the dorsum and under her tongue.

She was placed on 20,000 units of penicillin every three hours until 100,000 units had been given. Improvement in her mouth began at once and progressed steadily so that, after ten days, her gums, tongue, and tonsils were practically healed.

HERPETIC STOMATITIS

Herpetic stomatitis may be seen in any age group. It is associated in many instances with herpes labialis or with herpes simplex, but it may occur independently. Small ulcerations are observed, singly or in clusters, on the buccal mucosa on either side in the region of the soft palate, and on the posterior pharyngeal wall. A yellow exudate, as a rule, covers the necrotic areas. There may be a concomitant Vincent's infection with swollen, bleeding gums. Vincent's organisms can be recovered from the gums but rarely from the ulcers themselves. Pain on swallowing is common and there is marked loss of appetite.

R. S., a 4-year-old-boy, who had been sick with high fever the week before, was brought in by his mother because of "sores in his mouth and throat." He had a typical herpetic stomatitis, which responded promptly to penicillin therapy. He was given 20,000 units intramuscularly, every three hours, until 100,000 had been administered. The ulcerations in his mouth healed completely in five days.

COMMENT

When such common mouth infections as thrush, trench mouth, and herpetic stomatitis become severe, it seems that our usual armamentarium of drugs does very little in effecting an early cure. It is true that the old standbys, such as 1 or 2 per cent gentian violet, boric and peroxide irrigations, glycerite of boroglycerin, sodium perborate, cure the vast majority of the simpler infections of this character in a reasonable number of days. However, in the severe or protracted cases of thrush or Vincent's infection, the usual treatment drags on for days and even weeks, wearing out the patience of both the doctor and mother—and the poor patient, too. It is in these instances that the use of penicillin

is invaluable because of the rapidity with which it brings about an amelioration of symptoms.

Penicillin may be used topically in dilutions of 250 units per cubic centimeter in young infants or older children when it is not desirable to carry out the injection technique. Although this method seems a little slower than the intramuscular route, the results are as good, and certainly, the method is more effective than the former procedures of using dyes, oxidizing reagents, and mild and strong antiseptics. The intramuscular route should be preferred in the administration of penicillin, especially in severe cases. It is seldom that more than four or five deep injections are required, and these can all be given within a period of twelve to fifteen hours.

From an experience in treating a number of infants and children with the oral lesions described, I am convinced that penicillin now supersedes all hitherto-employed remedies as being the most reliable and effective. There were no untoward reactions or manifestations in the cases treated thus far.

SUMMARY

The treatment of severe thrush, Plaut-Vincent's infection, and herpetic stomatitis with the use of penicillin is discussed. The average treatment period of the severe case is seldom longer than a week, particularly when the drug is given by injection. With topical administration, the treatment time is slightly longer.

311 Lincoln Road

ACUTE POLIOMYELITIS AND ACUTE INFECTIOUS LYMPHOCYTOSIS

Their Apparent Simultaneous Occurrence in a Summer Camp

Jerome S. Beloff, M.D., and Kenneth M. Gang, M.D.
New York, N. Y.

THE diagnostic difficulties encountered during an epidemic of poliomyelitis are well exemplified by what occurred recently in a children's camp in Connecticut. Several cases of illness from that camp are reported because of the important differential diagnosis involved. Within a period of fourteen days a child became ill with meningoencephalitis resembling bulbar poliomyelitis; a second, with poliomyelitis suggestive of mumps encephalitis; a third, with apparently acute infectious lymphocytosis; and a fourth, with probable infectious lymphocytosis with associated paralysis, resembling poliomyelitis.

CASE REPORTS

Case 1.—A 4-year-old boy had been sick for two days with high fever and rapid respirations at the camp in Connecticut when he was admitted to the Charlotte Hungerford Hospital in Torrington, Conn. He had received sulfadiazine before admission to the hospital with little or no effect on the clinical course. The physical examination revealed nuchal rigidity, and a lumbar puncture was immediately performed. The fluid was water-clear and the pressure was 400 mm. of water. The total cell count was 79 leucocytes per cubic millimeter with 27 polymorphonuclear cells and 52 lymphocytes. The globulin was not increased. No organisms were seen in the smear, and cultures of the fluid were bacteriologically negative. The following day another lumbar puncture was done with similar findings. The urine was normal; the blood hemoglobin was 70 per cent; the white blood cells were 8,900 per cubic millimeter with 72 per cent neutrophiles and 28 per cent lymphocytes. The following day the white cell count was 7,000 per cubic millimeter. The blood culture was sterile.

The patient's elevated temperature decreased progressively after admission and was practically normal at the end of twenty-four hours. With the fall in temperature the pulse and respirations also decreased. On the second day the temperature was normal, pulse was 90, and respirations were 40 per minute. The lungs were clear to percussion and auscultation. The following morning the patient suddenly became cyanotic and acutely dyspneic. He was immediately placed in an oxygen tent, but despite this he died shortly thereafter.

The fulminating nature of this patient's illness, with the respiratory difficulty and meningeal signs, the normal white blood count, the moderate spinal fluid pleocytosis, and negative bacteriological studies made the diagnosis of bulbar poliomyelitis most tenable.

Case 2.—E. B. was a 6½-year-old girl who entered the Mount Sinai Hospital in New York City because of fever and headache of one day's duration. Her own past history was noncontributory, although she was exposed to a grandparent with active pulmonary tuberculosis until two

From the Pediatric Service of Murray H. Bass, M.D., Mount Sinai Hospital.

years before admission. Since that time, chest examinations and skin tests had been negative for tuberculosis. She had spent several weeks at the camp in Connecticut and had associated with the patient reported in Case 1. Three weeks previously there had been a small epidemic of diarrhea of unidentified origin at the camp, and ten days previously two children had developed mumps. The patient with bulbar poliomyelitis had become sick one week before this present illness.

One week before admission, the child had a mild upper respiratory infection which lasted several days. On the day before admission, she had a severe headache, loss of appetite, and fever of 101° F. in the morning. By evening the fever had risen to 102.4° F., but the symptoms had subsided. During that day she also had had four or five loose, nonbloody bowel movements, vomited once, and had developed a slight stiff neck. By morning her temperature was 104° F., she had a few loose stools, tremor of the hands, and a definite stiff neck. She was brought to Mount Sinai Hospital where a physical examination revealed the following:

She was a well-developed and well-nourished young girl appearing weak and febrile (temperature 104° F.). Her sole complaint was a stiff neck. The eyes were normal except for slight engorgement of the retinal veins. The nose and throat were normal. The uvula and palate moved well and evenly. There was slight but disinct nuchal rigidity. The chest showed good respiratory excursions, and her lungs were clear. The heart was normal, except for a soft systolic murmur at the apex. Abdominal examination revealed normal findings. There were no skin lesions. The deep tendon reflexes were hypoactive bilaterally but were all present. The superficial reflexes were normal, and there were no pathological reflexes. Except for a slight right facial weakness, there were no paralyses. Kernig and Brudzinski signs were not present.

Laboratory Examinations: Lumbar puncture revealed normal pressure and clear fluid, which on microscopic examination was found to contain 50 cells per cubic millimeter, mostly mononeulear cells. Pandy test was positive. The spinal fluid sugar was 33 milligrams per cent; protein, 36 milligrams per cent. Smear and culture of the spinal fluid were bacteriologically negative. The white blood count on admission was 45,000 per cubic millimeter with 90 per cent normal mature lymphocytes and 10 per cent polynuclear cells. The urine was normal. Tuberculin patch test was positive, but chest roentgenogram revealed nothing pathological. The blood culture was sterile. The blood Wassermann was negative. Heterophile agglutination test was negative on admission and again on the fifth hospital day. There were no demonstrable blood agglutinins for *Brucella abortus* or melitensis, the ten strains of dysentry organisms regularly tested for in our laboratories, typhoid, paratyphoid A or B, or proteus X_{19}. Complement fixation and mouse and guinea pig brain inoculation studies of blood and spinal fluid did not reveal findings of lymphocytic choriomeningitis.

On the day after admission, the temperature fluctuated between 100 and 101° F. All symptoms had disappeared. The temperature was normal thenceforth, and the patient remained asymptomatic except for a slight right calf pain, transient in nature, on the thirteenth hospital day. A spinal tap on the third day revealed clear fluid, positive Pandy test, a few fresh red blood cells, no white blood cells, smear negative for organisms, and protein 56 milligrams per cent. The white blood count that day showed 42,000 cells per cubic millimeter, with 74 per cent mature lymphocytes. By the fourth day, it was 56,000 per cubic millimeter with 72 per cent lymphocytes. On the fifth day, blood studies by a member of the hematological department showed a hemoglobin of 70 per cent; red blood cell count, 4,120,000 per cubic millimeter; platelets, 260,000; and white blood cells, 50,600 per cubic millimeter with 11 per cent segmented and 1 per cent nonsegmented polymorphonuclears, 4 per cent eosinophiles, 3 per cent monocytes, and 81 per cent mature

small lymphocytes. The bone marrow obtained by sternal aspiration was normal. By the eleventh hospital day the white blood count was 26,400 with 70 per cent lymphocytes, and on the twentieth day, 9,000 with 51 per cent lymphocytes. She was discharged, well, shortly thereafter.

In view of these findings, several possible diagnoses were considered in the differential diagnosis. Acute nonparalytic poliomyelitis was first considered because of the evidence of central nervous system involvement and the occurrence of poliomyelitis in the same camp (Case 1). As the blood findings were more unusual than have ever been recorded in that disease, that diagnosis was abandoned. The diagnosis of lymphocytic choriomeningitis was untenable in view of the blood picture and negative virus studies. Mumps or other infectious meningoencephalitis was ruled out by the clinical picture. Central nervous involvement is not uncommon with insignificant involvement of the parotid gland. A lymphocytosis of 50,000, however, is rarely found in such diseases. The rapid recovery and negative chest roentgenogram rendered the diagnosis of tuberculous meningitis impossible, despite the history of exposure and the positive patch test. Infectious mononucleosis was considered and ruled out by the absence of palpable glands or spleen, negative Paul-Bunnell test, very high leucocytosis, and by the normal appearance of the lymphocytes and bone marrow. Although the clinical manifestations of this patient were unusual for acute infectious lymphocytosis, they have been reported, and the course and laboratory findings were compatible with this diagnosis. Acute infectious lymphocytosis, therefore, was considered to be the most likely diagnosis.

At approximately the same time as this child's illness, another camper developed a clinical picture similar to this one with a high leucocytosis, predominantly lymphocytic, and central nervous system signs and symptoms resembling acute infectious lymphocytosis. There later developed paralyses suggestive of poliomyelitis. The details of this patient's illness are to be published in a separate communication from Grasslands Hospital in Valhalla, N. Y.

Case 3.—T. C., was a 12-year-old boy who had been previously well and was attending the same camp as the children already described. For three days before admission to the hospital the patient complained of nausea, vomiting, headache, stiff neck, and stiff back, and had fever of 102°F. On admission to the Willard Parker Hospital in New York City on August 12, the temperature was 103.2° F. The positive physical findings were moderate nuchal rigidity, a rigid back, and tenderness over the region of the parotid glands. The neurological examination revealed positive Kernig and Brudzinski reflexes bilaterally, and slightly hyperactive knee jerk and ankle jerk reflexes on the left.

The spinal fluid was clear, of normal pressure, and contained 141 cells per cubic millimeter, 90 per cent of which were polynuclear and 10 per cent, lymphocytic. The hemoglobin was 85 per cent; the white blood count, 7,050 on admission and 5,500 two days later, with polymorphonuclear cells 37 per cent, lymphocytes 57 per cent, and eosinophiles 6 per cent. The urine was normal.

The hospital course was uneventful as the nuchal rigidity, rigid back, and parotid tenderness were present only forty-eight hours. At the time of discharge the child was able to walk without difficulty, but the Kernig reflexes were still questionable, and there was slight spasm of the gastrocnemii muscles and flexor muscles of the thighs.

The discharge diagnosis was acute anterior poliomyelitis, nonparalytic, as all but one of the features of the illness were classical of that disease. However, the parotid tenderness was a confirmed finding which could not be easily discounted. A mumps infection with associated mumps meningoencephalitis could also be accepted as a diagnostic possibility, particularly as there were two children with mumps at the same camp several weeks previously. A final opinion is difficult to make in retrospect, as no virus studies or blood agglutination studies were performed.

DISCUSSION

These four patients are particularly interesting in the diagnostic problems that they present, because of their unusual clinical manifestations. The first child presented a syndrome best explained by the diagnosis of bulbar poliomyelitis. The second patient became ill one week later with a clinical picture resembling acute infectious lymphocytosis, the disease entity recently described by Smith.[1] However, were it not for the extreme leucocytosis and relative lymphocytosis, the diagnosis of nonparalytic poliomyelitis could have been made. Two days after the onset of this illness a third child developed what appeared to be another example of infectious lymphocytosis with the blood picture of that disease, but six days later she was suddenly afflicted with multiple paralyses of arms and legs, as are seen in poliomyelitis. At about the same time the fourth patient developed all of the clinical and laboratory criteria of acute nonparalytic poliomyelitis except for definite tenderness of the parotid glands. This finding strongly suggested the possibility of a mumps meningoencephalitis. Unfortunately, further differential diagnostic procedures were not obtainable.

It is not the purpose of this communication to discuss the differential diagnosis of diseases confused with poliomyelitis. This has been adequately presented by Brahdy and Lenarsky,[2] and also by Landon,[3] in their discussion of the poliomyelitis epidemic of 1931 in New York City. We are interested here in the relationship of acute infectious lymphocytosis and acute poliomyelitis to the unusual clinical manifestations of our second patient.

Smith[1] in 1941 described as an entity, acute infectious lymphocytosis, a disease differing from infectious mononucleosis both from a clinical and laboratory standpoint.

Atypical examples of infectious mononucleosis had long been recognized, and Thelander and Shaw[6] suggested that these atypical examples might not be the same disease at all. A series of sixteen such patients were reported by Reyersbach and Lenert,[4] in an epidemic at Irvington House, in which there were no clinical symptoms or physical signs, but in which routine blood studies showed very high white blood counts with lymphocytic predominance and invariably negative heterophile agglutinations.

It remained for Smith, however, to describe accurately the features of this disease and to set up criteria for diagnosis. The clinical manifestations are protean. There may be no symptoms at all, as was the case with Reyersbach and Lenert's series. There may be symptoms of upper respiratory infection of lesser or greater severity, including fever.

Many other organ systems may be involved. Abdominal symptoms are often present. There was no lymphadenopathy or splenomegaly in any of Smith's patients.

The characteristic white blood count is very high, usually much higher than is found with infectious mononucleosis. It is generally about 50,000 per cubic millimeter but may be elevated above 100,000. The differential count shows predominantly lymphocytes, which may constitute a bare majority or make up 90 per cent of the total white cell count. Morphologically they cannot be distinguished from normal mature lymphocytes. Whereas, the white blood cells in infectious mononucleosis have irregular staining properties, peculiarly-shaped and light-staining nuclei, and foamy or vacuolated cytoplasm, the cells of infectious lymphocytosis are small, with dark, regular nuclei, and clear homogeneous cytoplasm.

The Paul-Bunnell heterophile agglutination test is within normal limits in infectious lymphocytosis. The bone marrow examination is said by Smith to show perfectly normal marrow, except for possible increase in adult lymphocytes. Smith[5] recently studied biopsied lymph nodes from two patients with infectious lymphocytosis and considered the histologic picture unique.

Although most of the patients described were children, contact studies revealed adult infection also. Apparently quite contagious, the disease spread readily to family and hospital contacts, with a probable incubation period of from twelve to twenty-one days. The course was invariably benign in the examples reported. When symptoms were present, they subsided in one or two days. The fever always subsided rapidly, occasionally continuing at low grade for a short while. Laboratory evidence of the disease persisted for four to five weeks.

Thelander and Shaw[6] described two patients with what they believed might be infectious mononucleosis, who were strikingly similar to our second patient. Two siblings, 2½ and 3½ years old, were described, with meningeal and encephalitic signs of moderate severity and short duration. Laboratory studies revealed 16 and 44 mononuclear cells per cubic millimeter of spinal fluid, and white blood counts of 56,000 with 82 per cent lymphocytes, and 50,000 with 84 per cent lymphocytes. Heterophile agglutinations were negative or within normal limits. There were no palpable glands or spleen. Smith[1] considered these to be examples of infectious lymphocytosis.

The simultaneous occurrence in one epidemic area of poliomyelitis and infectious lymphocytosis raises several questions. These patients with lymphocytosis may have had poliomyelitis with unusual blood reactions, or they may represent the disease described by Smith, acute infectious lymphocytosis. A third possibility would be the simultaneous occurrence of the two infections in the same epidemic area, appearing in pure form in some patients and possibly combined in others. It is a well-known fact that two distinct virus diseases may coexist in one epidemic. In survey reports of white blood counts in poliomyelitis epidemics, the counts are reported as normal or occasionally as high as 30,000, with a normal differential count or slight polymorphonuclear leucocytosis.[7] We have been unable to find in the literature instances of poliomyelitis with white blood cell counts as high as those found in our second and

third patients. On the other hand, of the patients reported by Smith none had clinical manifestations predominantly of central nervous system origin. Our second case, however, resembles those of Thelander and Shaw described previously, which, Smith believes, fall into his classification of infectious lymphocytosis. The third child, reported with associated paralysis, has no counterpart in any reported examples of that disease. The blood picture is typical of infectious lymphocytosis and atypical of poliomyelitis. The paralyses are such as would be expected with poliomyelitis and have never been described with infectious lymphocytosis.

In the 1934-1935 epidemic of poliomyelitis in Southern California, atypical clinical forms were noted by Wilson and Walker[8] in adults as compared with the usual nature of the disease in the children. The unusual clinical pattern in the adult group presented a diagnostic problem, similar to that raised by our study, which was never completely resolved. Kessel and associates[9] studied a poliomyelitis virus strain from one of the fatal cases from that epidemic and found a definite difference in paralysis rate, recovery rate, and histopathology in monkeys inoculated with that virus as compared with a strain obtained from the Rockefeller Institute. This suggests the possibility of atypical clinical forms of the disease on the basis of different strains of the poliomyelitis virus.

The whole question of the classification of these unusual diseases awaits bacteriologic investigation of the causative organism. Because of war conditions we were unable to obtain virus studies on our patients. No organism has consistently been isolated in infectious lymphocytosis. That disease is quite contagious and viral etiology is consequently suspected. Infectious lymphocytosis might possibly represent an atypical clinical form of poliomyelitis, on the basis of different strains of the poliomyelitis virus. When the organism is found, it will have to be studied as to its relations with the virus, or viruses, of poliomyelitis, to solve the present problem. Until that is done, the validity of acute infectious lymphocytosis as a separate disease entity will have to remain a question, and the diagnostic problem raised by our patients must remain unsolved.

SUMMARY

1. Three illnesses from one children's camp in Connecticut are reported in detail. Two are apparently poliomyelitis. The other, occurring at approximately the same time, has clinical manifestations of poliomyelitis with unusually marked leucocytosis and lymphocytosis as is seen in acute infectious lymphocytosis.

2. A brief review of the subject of infectious lymphocytosis is presented, with its differential diagnosis.

3. The possible significance of the association in one epidemic area of poliomyelitis and acute infectious lymphocytosis is discussed.

The authors wish to take this opportunity to express their indebtedness to Dr. Jerome Kohn for his advice in preparing the manuscript, and to Dr. C. H. Turkington of Litchfield, Conn., and Dr. Irving Klein of New York for permission to publish data on their cases.

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Erratum

In the article by Hogg and Bradley entitled "Pneumococcus in the Newborn" in the April, 1945, issue of the JOURNAL on page 408, line 31, the sentence should read as follows: "Total sulfadiazine given was 9.25 Gm. over a period of fifteen days."

News and Notes

The following were certified by the *American Board of Pediatrics* following New York examinations March 29 to 31, 1945:

Dr. Olga E. Allers, 1101 Beacon Street, Brookline, Mass.

Dr. Ben Arbor, 3136 Perry Avenue, New York 67, N. Y.

Dr. Hans Behrendt, 1165 Park Avenue, New York, N. Y.

Dr. John Kincaid Brines, 29 Martin Road, Wellesley, Mass. (Now Captain, United States Army, Army Air Forces Regional Hospital, Eglin Field, Fla.)

Dr. Ethel G. Cermak, 516 Madison Avenue, Albany 3, New York

Dr. Joseph Alfred Costa, North Bedford Road, Bedford Hills, N. Y.

Dr. Robert Downing Cox, Belmont Hospital, Worcester 5, Mass.

Dr. Leon N. Goldenberg, 255 Eastern Parkway, Brooklyn, N. Y.

Dr. Daniel C. Hackett, Riverdale, New York City, N. Y. (Now in United States Public Health Service, P.O. Box 426, Elizabeth City, N. C.)

Dr. Robert Norton Ganz, 19 Bay State Road, Boston, Mass. (Now Lieutenant Commander, United States Naval Reserve, 7 Waterhouse Street, Cambridge, Mass.)

Dr. Paul Theodore Hahman, 760 Market Street, San Francisco, Calif. (Now Captain, United States Army, Station Hospital, Camp Crowder, Mo.)

Dr. Olga Haller, 182 Roseville Avenue, Newark 7, New Jersey

Dr. Sarah Hooker Hardwicke, New York Hospital, 525 E. 68th Street, New York 21, N. Y.

Dr. Elizabeth B. Hinckley, 90 Morningside Drive, New York 27, N. Y.

Dr. Elizabeth A. Jackson Ittner, 182 Clinton Street, Brooklyn, N. Y.

Dr. Dorothy Steinle Jaeger, 2146 Wyoming Avenue, N. W., Washington 8, D. C.

Dr. Herman B. Katzman, 665 Ocean Parkway, Brooklyn 30, N. Y.

Dr. Vincent de Paul Larkin, 1060 Park Avenue, New York 28, N. Y.

Dr. Henry Foster Lee, Eighteenth and Bainbridge Streets, Philadelphia 46, Pa.

Dr. Virginia Catherine Lent, 359 Front Street, Hempstead, N. Y.

Dr. Luigi Luzzatti, New York Hospital, 525 E. Sixty-Eighth Street, New York 21, N. Y.

Dr. James H. Maroney, 129 Summit Avenue, Summit, New Jersey. (Now Lieutenant, United States Naval Reserve, United States Naval Academy, Annapolis, Md.)

Dr. Leonard Montag, Port Arthur, Texas. (Now Lieutenant, United States Army, Station Hospital, Fort Miles, Del.)

Dr. Dario Morelli, 40 Avon Street, Wakefield, Mass.

Dr. Frances Pizitz, 27 West Ninety-Sixth Street, New York, N. Y.

Dr. Ralph Lewis Prowda, 713 E. Genesee Street, Syracuse, N. Y.

Dr. Benjamin Owen Ravenel, Medical College of State of South Carolina, Charleston, S. C.

Dr. William Lacy Rumsey, Jr., 399 Westfield Avenue, Elizabeth, N. J.

Dr. William Morris Schmidt, Children's Bureau, United States Department of Labor, Washington 25, D. C.

Dr. Lois M. Smedley, 1 Ascan Avenue, Forest Hills, N. Y.

Dr. John Hostley Soady, Sunset Avenue, Asheboro, North Carolina

Dr. Jack Tepper, O.S.S.O. Home, Xenia, Ohio

Dr. Clara Waldinger, 17 Moraine Street, Jamaica Plain, Mass.

Dr. David Louis Weinstein, 5030 Sixteenth Street, N. W., Washington 11, D. C.

Dr. Dorothy Vermilya Whipple, 3821 Woodley Road, N. W., Washington, D. C.

Dr. Louis Arnold Wikler, 151 W. Susquehanna Avenue, Philadelphia, Pa. (Now Lieutenant, United States Naval Reserve, U. S. Naval Hospital, Jacksonville, Fla.)

At this examination fifty-four candidates were examined. Thirty-six were passed and certified. Seventeen failed and one was conditioned in Growth and Development.

The total number of pediatricians certified by the Board including the above is 2,354.

The *American Board of Pediatrics* announces the following dates for the fall examination:

Written examination: locally under a monitor Oct. 19, 1945.

Oral examination: New York City, Dec. 7 or 8, 1945.

The deaths of the following Fellows have been reported to the JOURNAL:

Dr. Louis Fischer of New York, April 9, 1945.

Dr. William A. Mulherin, of Augusta, Ga., April 9, 1945.

Dr. Angus B. Cowan of Fresno, Calif., March, 1945.

The Pediatrician and the War

Captain John W. Canady, Glen Falls, N. Y., has been promoted to Major.

Captain A. S. Finkelstein of Newark, N. J., has been promoted to Major.

Dr. Elizabeth Brakeley of Montclair, N. J., has been commissioned as Major in the United States Public Health Service.

Announcement

In compliance with the directives imposed by the War Production Board limiting the amount of paper consumed in the production of this JOURNAL, the publishers find it necessary to change the format. As soon as these restrictions are lifted the original format will be restored. Even though the number of pages has been reduced, the actual content of the JOURNAL has not been decreased to any appreciable extent.

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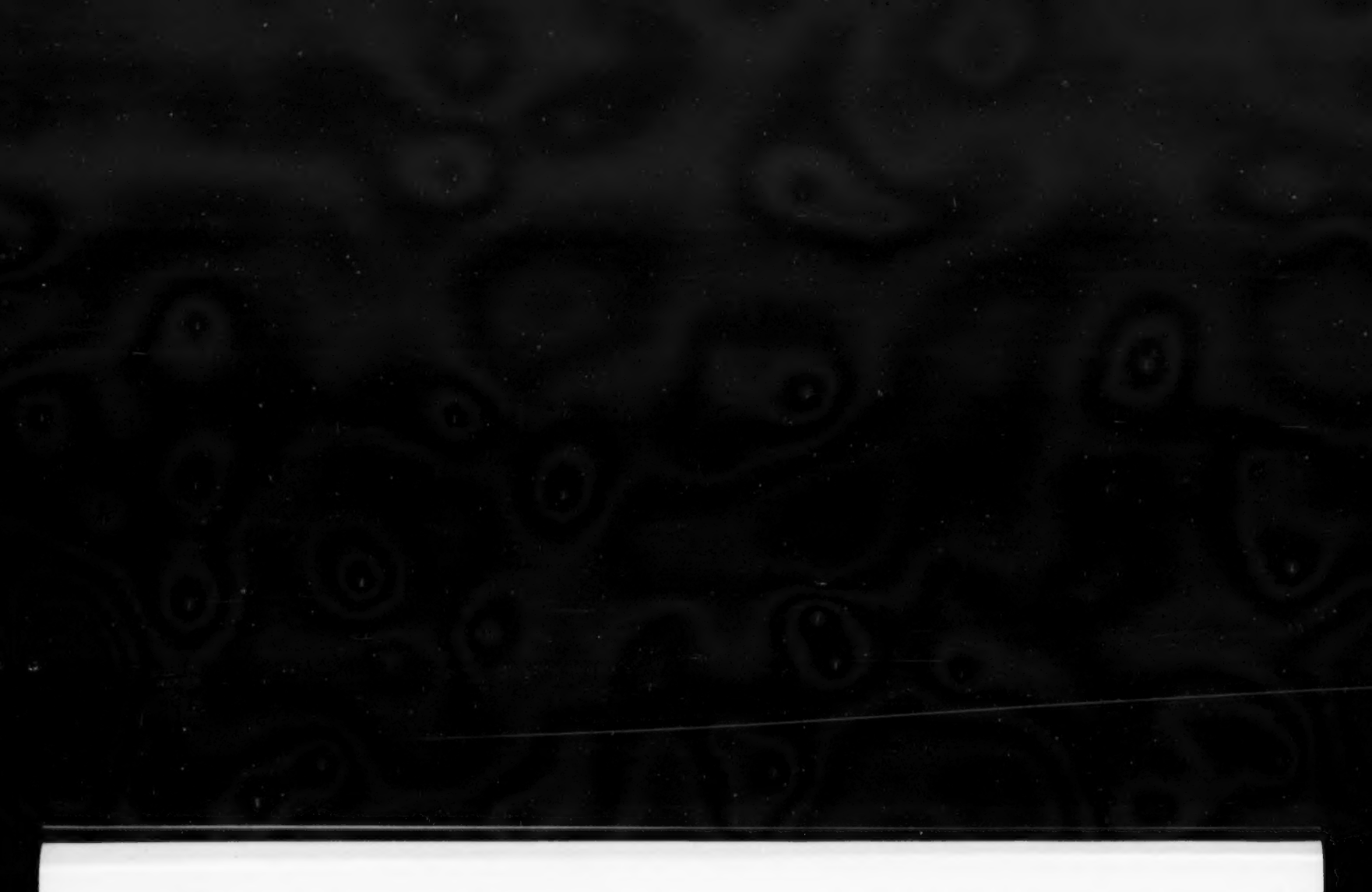

INDEX NUMBER

Vol. 26 JUNE, 1945 No. 6

THE JOURNAL OF PEDIATRICS

A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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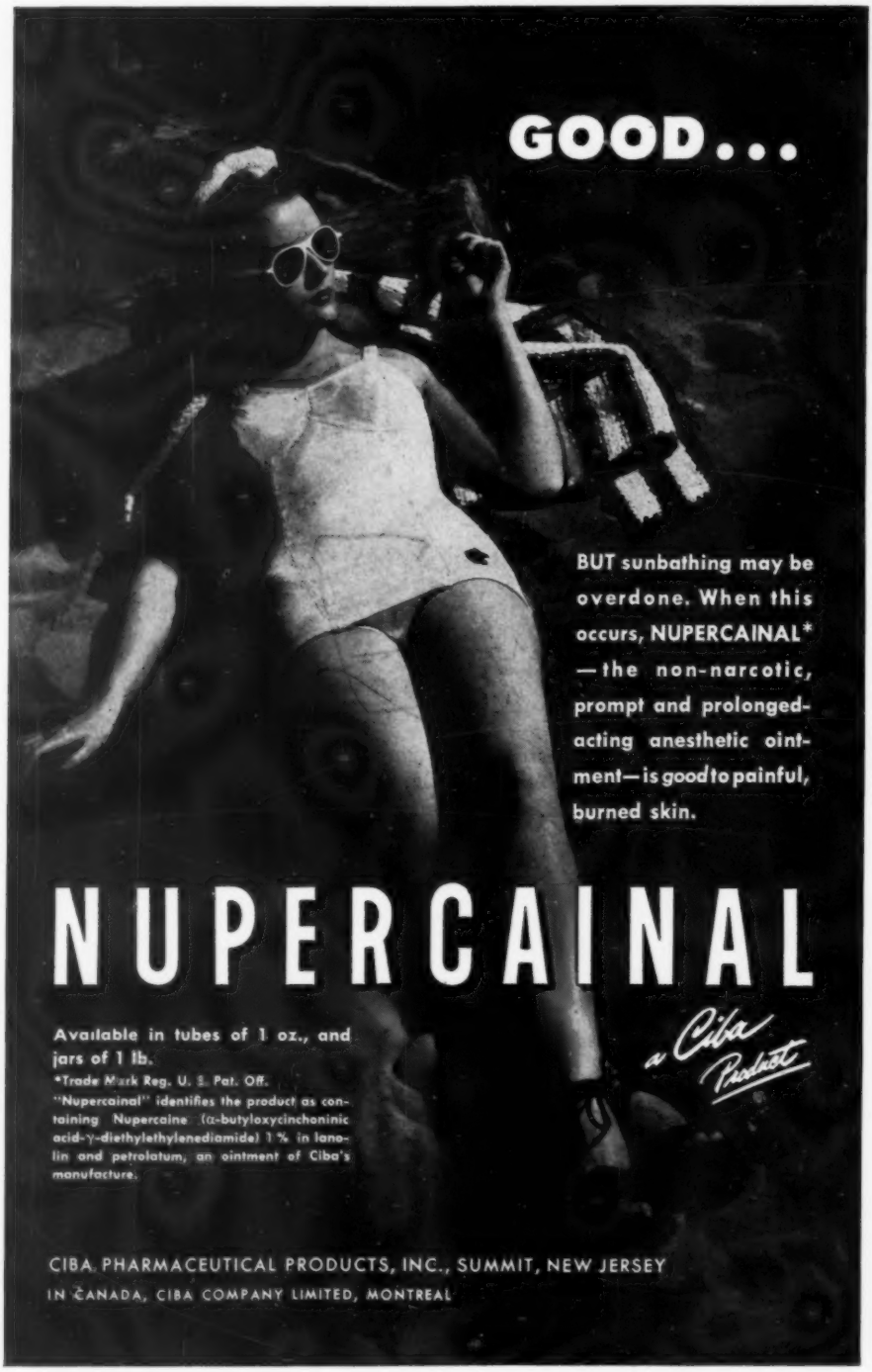
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Vol. 26, No. 6, June, 1945. The Journal of Pediatrics is published Monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription price: United States, its possessions, Pan-American Countries, $8.50 a year; Canada, $10.00 (Canadian Currency); Foreign, $9.50. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.